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[Intervention Review]

Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

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A B S T R A C T

Background

Long-acting bronchodilators such as long-acting β-agonist (LABA), long-acting muscarinic antagonist (LAMA), and LABA/inhaled corticosteroid (ICS) combinations have been used in people with moderate to severe chronic obstructive pulmonary disease (COPD) to control symptoms such as dyspnoea and cough, and prevent exacerbations. A number of LABA/LAMA combinations are now available for clinical use in COPD. However, it is not clear which group of above mentioned inhalers is most effective or if any specific formulation works better than the others within the same group or class.

Objectives

To compare the efficacy and safety of available formulations from four different groups of inhalers (i.e. LABA/LAMA combination, LABA/ICS combination, LAMA and LABA) in people with moderate to severe COPD. The review will update previous systematic reviews on dual combination inhalers and long-acting bronchodilators to answer the questions described above using the strength of a network meta-analysis (NMA).

Search methods

We identified studies from the Cochrane Airways Specialised Register, which contains several databases. We also conducted a search of ClinicalTrials.gov and manufacturers' websites. The most recent searches were conducted on 6 April 2018.

Selection criteria

We included randomised controlled trials (RCTs) that recruited people aged 35 years or older with a diagnosis of COPD and a baseline forced expiratory volume in one second (FEV1) of less than 80% of predicted. We included studies of at least 12 weeks' duration including at least two active comparators from one of the four inhaler groups.

Data collection and analysis

We conducted NMAs using a Bayesian Markov chain Monte Carlo method. We considered a study as high risk if recruited participants had at least one COPD exacerbation within the 12 months before study entry and as low risk otherwise. Primary outcomes were COPD exacerbations (moderate to severe and severe), and secondary outcomes included symptom and quality-of-life scores, safety outcomes, and lung function. We collected data only for active comparators and did not consider placebo was not considered. We assumed a class/group effect when a fixed-class model fitted well. Otherwise we used a random-class model to assess intraclass/group differences. We supplemented the NMAs with pairwise meta-analyses.

Main results

We included a total of 101,311 participants from 99 studies (26 studies with 32,265 participants in the high-risk population and 73 studies with 69,046 participants in the low-risk population) in our systematic review. The median duration of studies was 52 weeks in the high-risk population and 26 weeks in the low-risk population (range 12 to 156 for both populations). We considered the quality of included studies generally to be good.

The NMAs suggested that the LABA/LAMA combination was the highest ranked treatment group to reduce COPD exacerbations followed by LAMA in the both populations.

There is evidence that the LABA/LAMA combination decreases moderate to severe exacerbations compared to LABA/ICS combination, LAMA, and LABA in the high-risk population (network hazard ratios (HRs) 0.86 (95% credible interval (CrI) 0.76 to 0.99), 0.87 (95% CrI 0.78 to 0.99), and 0.70 (95% CrI 0.61 to 0.8) respectively), and that LAMA decreases moderate to severe exacerbations compared to LABA in the high- and low-risk populations (network HR 0.80 (95% CrI 0.71 to 0.88) and 0.87 (95% CrI 0.78 to 0.97), respectively). There is evidence that the LABA/LAMA combination reduces severe exacerbations compared to LABA/ICS combination and LABA in the high-risk population (network HR 0.78 (95% CrI 0.64 to 0.93) and 0.64 (95% CrI 0.51 to 0.81), respectively).

There was a general trend towards a greater improvement in symptom and quality-of-life scores with the combination therapies compared to monotherapies, and the combination therapies were generally ranked higher than monotherapies.

The LABA/ICS combination was the lowest ranked in pneumonia serious adverse events (SAEs) in both populations. There is evidence that the LABA/ICS combination increases the odds of pneumonia compared to LAMA/LABA combination, LAMA and LABA (network ORs: 1.69 (95% CrI 1.20 to 2.44), 1.78 (95% CrI 1.33 to 2.39), and 1.50 (95% CrI 1.17 to 1.92) in the high-risk population and network or pairwise OR: 2.33 (95% CI 1.03 to 5.26), 2.02 (95% CrI 1.16 to 3.72), and 1.93 (95% CrI 1.29 to 3.22) in the low-risk population respectively). There were significant overlaps in the rank statistics in the other safety outcomes including mortality, total, COPD, and cardiac SAEs, and dropouts due to adverse events.

None of the differences in lung function met a minimal clinically important difference criterion except for LABA/LAMA combination versus LABA in the high-risk population (network mean difference 0.13 L (95% CrI 0.10 to 0.15). The results of pairwise meta-analyses generally agreed with those of the NMAs. There is no evidence to suggest intraclass/group differences except for lung function at 12 months in the high-risk population.

Authors' conclusions

The LABA/LAMA combination was the highest ranked treatment group to reduce COPD exacerbations although there was some uncertainty in the results. LAMA containing inhalers may have an advantage over those without a LAMA for preventing COPD exacerbations based on the rank statistics. Combination therapies appear more effective than monotherapies for improving symptom and quality-of-life scores. ICS-containing inhalers are associated with an increased risk of pneumonia.

Our most comprehensive review including intraclass/group comparisons, free combination therapies, 99 studies, and 20 outcomes for each high- and low-risk population summarises the current literature and could help with updating existing COPD guidelines.

PLAIN LANGUAGE SUMMARY

Which long-acting inhalers are the most effective and safest for people with advanced chronic obstructive pulmonary disease (COPD)?

What is COPD and why does a doctor prescribe an inhaler?

Chronic obstructive lung disease (COPD) is usually caused by smoking or other airway irritants. COPD damages the lungs and causes airways to narrow which makes it difficult to breathe.

There are two types of inhalers for COPD: rescue and maintenance. A rescue inhaler is short- and fast-acting, and used as needed for quick relief of symptoms, whereas a maintenance inhaler is long-acting and used on a daily basis to relieve daily symptoms and reduce flare-ups. The long-acting inhalers are usually reserved for more advanced COPD.

Does it matter which long-acting inhaler is used in people with advanced COPD?

Commonly used maintenance inhalers are grouped into four different groups: long-acting beta2-agonists (LABAs); long-acting muscarinic antagonists (LAMAs); LABA/inhaled corticosteroid (ICS) combinations; and LABA/LAMA combinations. Combination inhalers are usually reserved for individuals whose single-maintenance inhaler, such as LAMA or LABA fails. There are not many head-to-head comparisons to determine which treatment group or individual inhaler is better compared to the others. Preventing severe flare-ups and hospital admissions is especially important to people with COPD, healthcare providers, policy makers and society.

How did we answer the question?

We collected and analysed data from 99 studies, including a total of 101,311 participants with advanced COPD, using a special method called network meta-analysis, which enabled us to simultaneously compare the four inhaler groups and 28 individual inhalers (4 LABAs, 5 LAMAs, 9 LABA/ICS combinations, and 10 LABA/LAMA combinations).

What did we find?

The LABA/LAMA combination was the best treatment, followed by LAMA, in preventing flare-ups although there was some uncertainty in the results. Combination inhalers (LABA/LAMA and LABA/ICS), are more effective for controlling symptoms than single-agent therapies (LAMA and LABA), in general. The LABA/LAMA combination was better than LABA/ICS combination, especially in people with a prior episode of flare-ups. The LABA/ICS combination had a higher incidence of severe pneumonia compared to the others. We did not find a difference in benefits and harms, including side effects, among individual inhalers within the same treatment groups.

Conclusion

The LABA/LAMA combination is likely the best treatment in preventing COPD flare-ups. LAMA-containing inhalers appear to have an advantage over those without LAMA for preventing flare-ups. Combination inhalers (LABA/LAMA and LABA/ICS), appear more effective for controlling symptoms than single-agent therapies (LAMA and LABA). Inhaled steroids carry an increased risk of pneumonia.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

LABA/LAMA compared to LABA/ICS for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease with predicted FEV1 of less than 80%
Setting: outpatient
Intervention: LABA/LAMA
Comparison: LABA/ICS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with LABA/ICS	Risk difference with LABA/LAMA			
Moderate to severe exacerbations: high-risk population	443 per 1000	34 fewer per 1000 (66 fewer to 0 fewer)	OR 0.87 (0.76 to 1.00)	3372 (1 RCT)	⊕⊕⊕○ Moderate[1,2]
Moderate to severe exacerbations: low-risk population	89 per 1000	11 fewer per 1000 (29 fewer to 11 more)	OR 0.86 (0.65 to 1.14)	4315 (6 RCTs)	⊕⊕⊕○ Moderate[1,3]
Severe exacerbations: high-risk population	172 per 1000	17 fewer per 1000 (39 fewer to 8 more)	OR 0.88 (0.74 to 1.06)	3354 (1 RCT)	⊕⊕⊕○ Moderate[1,3]
Severe exacerbations: low-risk population	17 per 1000	6 fewer per 1000 (12 fewer to 10 more)	OR 0.66 (0.27 to 1.63)	2860 (4 RCTs)	⊕⊕⊕○ Moderate[1,3]
Pneumonia: high-risk population	32 per 1000	12 fewer per 1000 (19 fewer to 1 fewer)	OR 0.62 (0.40 to 0.96)	3358 (1 RCT)	⊕⊕⊕○ Moderate[1]
Pneumonia: low-risk population	8 per 1000	4 fewer per 1000 (6 fewer to 0 fewer)	OR 0.43 (0.19 to 0.97)	5395 (7 RCTs)	⊕⊕⊕○ Moderate[1]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FEV1**: forced expiratory volume-one second; **ICS**: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **OR:** odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Optimal information size was not met.
[2]95% CI contains the line of no difference.
[3] We could not exclude the possibility of a clinically important difference due to a wide 95% CI.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a globally prevalent illness, characterised by chronic airway inflammation leading to slow progression of airflow limitation (GOLD 2018). The inflammatory nature of the disease leads to variable degrees of small airway obstruction and destruction of lung parenchyma. COPD accounts for more than three million deaths annually and is the third leading cause of death worldwide. This disease is due primarily to tobacco smoke in high-income countries; tobacco smoking is also the primary cause of COPD in low-income countries, but air pollution and indoor biomass fuel consumption are more frequent causes compared to high-income countries. The disease affects men and women equally (WHO 2016). Despite the worldwide prevalence of the disease, it remains largely under-recognised and underdiagnosed. COPD is a costly disease, with an estimated annual cost of USD 49.9 billion, including an indirect cost estimated at approximately 41% of the total cost in the USA and a total cost of EUR 38.7 billion in Europe (Patel 2014; WHO 2016). Clinically, the disease is characterised by chronic dyspnoea, productive cough and exposure to a risk factor such as smoking. The post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) is required to be less than 0.7 for this diagnosis (GOLD 2018). The disease course is usually interrupted by episodes of acute exacerbation, the frequency of which contributes to overall morbidity and mortality (Suissa 2012).

Description of the intervention

Management of stable COPD

Once COPD has been diagnosed, the main goals of therapy include alleviation of symptoms and prevention of disease progression and acute exacerbations. Smoking cessation is one of the most important non-pharmacological interventions. Annual influenza vaccination is recommended for everyone with COPD. In observational studies, influenza vaccination was associated with fewer outpatient visits, hospitalisations and deaths (Trucchi 2015). Pulmonary rehabilitation has been proven to improve exercise tolerance while reducing symptoms and exacerbations (McCarthy 2015; Rochester 2015). Inhaled medications, the mainstay of pharmacological therapies, are used to improve lung function, symptoms and quality of life, as well as to reduce acute exacerbations. Short-acting bronchodilators are given on an as-needed basis to provide immediate relief, and long-acting bronchodilators are used as maintenance therapy in people with moderate to very severe disease (Decramer 2012). The Global Initiative for Chronic Obstructive Lung Disease (GOLD), recommends long-acting bronchodilators as maintenance therapy in people experiencing long-term respiratory symptoms or exacerbations.(GOLD 2018).

How the intervention might work

Combination bronchodilators

Dual combination inhalers include long-acting beta-adrenoceptor agonist/inhaled corticosteroid (LABA/ICS) and LABA/long-acting muscarinic antagonist (LAMA) combinations. An ICS has anti-inflammatory effects and may reduce airway inflammation as well as systemic inflammation, as evidenced by a reduction in C-reactive protein (Heidari 2012). ICSs and LABAs have synergistic effects when used in combination. Corticosteroids upregulate beta$_2$-receptors and beta$_2$-agnoists and facilitate translocation of steroid receptors from the cytoplasm to the nucleus (Falk 2008). In vitro synergistic effects mentioned above may translate into clinical benefit. Clinical studies have suggested that a LABA/ICS combination significantly improved lung function, health status and rate of exacerbation compared with placebo, LABA alone or ICS alone (Nannini 2012).

Preclinical studies have suggested drug synergy between a beta$_2$-adrenoreceptor agonist and a muscarinic agonist. A possible mechanism for this synergism is that a muscarinic agonist causes less suppression of potassium channel opening, leading to relaxation of the airway smooth muscle, which further promotes beta$_2$-mediated smooth muscle relaxation by activating ion channels and other intracellular signalling pathways (Kume 2014). Clinical studies have demonstrated that LABA/LAMA combinations were superior to monotherapies with regard to lung function improvement and in a recent network meta-analysis (NMA), were associated with improved quality of life and symptom scores, and reduced COPD exacerbations as compared with LABA or LAMA alone (Oba 2016a).

Guidelines recommend a LABA/LAMA combination for people whose symptoms are not well controlled with a single long-acting bronchodilator, and a LABA/LAMA or LABA/ICS combination for those with frequent exacerbations (i.e. two or more exacerbations per year or one hospitalisation per year for an exacerbation). A LABA/LAMA combination may be preferred to a LABA/ICS combination, as ICSs are associated with increased risk of pneumonia (GOLD 2018; Oba 2016b; Wedzicha 2016).

Why it is important to do this review

Data on the efficacy and safety of LABA/LAMA combinations are accumulating (Huisman 2015; Oba 2016a; Schlueter 2016). However, an important clinical question is how do the efficacy and safety of LABA/LAMA combinations compare with those of LABA/ICS combinations for people with uncontrolled symptoms or frequent exacerbations, or both. Additional clinical studies, including several head-to-head studies comparing LABA/LAMA and LABA/ICS combinations (Donohue 2015; Singh 2015d; Vogelmeier 2013a; Vogelmeier 2015; Wedzicha 2016; Zhong 2015), have been published since an NMA comparing combination inhalers focused on studies up to December 2013 (Tricco 2015). Our review updates previous systematic reviews on dual combination inhalers and long-acting bronchodilators using the strength of an NMA.

OBJECTIVES

To compare the efficacy and safety of available formulations from four different groups of inhalers (i.e. LABA/LAMA combination, LABA/ICS combination, LAMA and LABA) in people with moderate to severe COPD. The review will update previous systematic reviews on dual combination inhalers and long-acting bronchodilators to answer the questions described above using the strength of a network meta-analysis (NMA).

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel, randomised controlled trials (RCTs), of at least 12 weeks' duration, published or unpublished. We did not consider cross-over studies.

Types of participants

We included studies that recruited people aged 35 years or older with a diagnosis of COPD, in accordance with American Thoracic Society-European Respiratory Society (ATS/ERS 2004), GOLD report (GOLD 2018), or equivalent criteria. Obstructive ventilatory defect should be at least moderate, with a baseline FEV1 less than 80% of predicted. We excluded studies that enrolled participants with a history of asthma or other respiratory disease.

Types of interventions

We included studies comparing at least two of the following therapies. We limited treatment arms to drug formulations and doses that were licensed in the USA or EU countries, or both, for clinical use. We did not consider triple combination therapy (i.e. LABA/LAMA/ICS) because it was out of scope for this review.

1. LAMA monotherapy
2. LABA monotherapy
3. Fixed-dose or free combination of LABA/ICS
4. Fixed-dose or free combination of LABA/LAMA

We allowed the use of a short-acting bronchodilator, such as salbutamol(also known as albuterol), and ipratropium as rescue treatment.

Types of outcome measures

Primary outcomes

1. COPD exacerbations (moderate to severe and severe)

Secondary outcomes

1. Change from baseline in St George's Respiratory Questionnaire (SGRQ) score and decrease in SGRQ score by 4 units or more (SGRQ responder)
2. Transition Dyspnea Index (TDI)
3. Mortality
4. Total serious adverse events (SAEs)
5. Cardiac and COPD SAEs
6. Dropouts due to adverse events
7. Change from baseline in trough FEV1
8. Pneumonia reported as SAE

We used an end-point score for dichotomous outcomes. For continuous outcomes, we used a change score reported at 3, 6, 12 months and the end of the study, when available. We defined 'moderate exacerbation' as worsening of respiratory status that requires treatment with systemic corticosteroids or antibiotics, or both; we defined 'severe exacerbation' as rapid deterioration that requires hospitalisation. The above-mentioned outcomes and their definitions are well established and widely used across the medical literature.

Search methods for identification of studies

Electronic searches

We identified studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Register contains trial reports identified through systematic searches of the following bibliographic databases:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies (CRS);
2. weekly searches of MEDLINE Ovid SP 1946 to date;
3. weekly searches of Embase Ovid SP 1974 to date;
4. Monthly searches of PsycINFO Ovid SP 1967 to date;

5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) 1937 to date;
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine) all years to date;
7. handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and manufacturers' websites. We searched all sources from their inception to 6 April 2018, and we imposed no restriction on language of publication.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for study information. We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and reported within the review the date this was done.

Data collection and analysis

Selection of studies

Two review authors (YO, NG) independently screened studies by title and abstract to evaluate whether a study met the inclusion and exclusion criteria. We selected studies that evaluated the clinical efficacy and safety of any of the following therapies in people with COPD: LABA/LAMA, LABA/ICS, LABA and LAMA. We resolved disagreements by involving a third contributor Joe V Devasahayam (JVD). We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

Two review authors (YO, NG), independently extracted information on study design, study size, population, interventions (drug, dose, inhaler type, allowed co-medications), severity of illness and end points of interest. We gathered information on whether a participant had been unsuccessfully treated with a long-acting bronchodilator before entry into clinical studies. We extracted and verified data from each of the existing reviews, which were cross-checked and verified by at least two review authors. We resolved disagreements regarding values, inconsistencies and uncertainties by involving a third contributor. Two review authors (YO, NG) independently extracted outcome data from the included studies. We noted in the 'Characteristics of included studies' table if outcome data were not reported in a useable way. We resolved disagreements by reaching consensus or by involving a third contributor (JVD). One review author (YO) transferred data into the Review Manager 5 file (Review Manager 2014). We double-checked that data had been entered correctly by comparing data presented in the systematic review versus study reports. A second review author (NG) spot-checked study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (YO, NG) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We resolved disagreements by discussion or by consultation with another contributor (JVD). We assessed risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised 'Risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may have been very different than for a patient-reported dyspnoea scale). When information on risk of bias related to unpublished data, we noted this in the 'Risk of bias' table. When considering treatment effects, we took into account the risk of bias for studies that contributes to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and reported deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

Network meta-analysis

We conducted NMAs using a Bayesian Markov chain Monte Carlo method and fitted in WinBUGS (version 1.4.3.), using code adapted from Dias 2018, which correctly accounts for correlations in studies with more than two arms and allows the specific data structures being considered. We compared each pair of treatments by estimating an odds ratio (OR) or hazard ratio (HR) for dichotomous outcomes, and a difference in mean or median for continuous outcomes, along with their 95% credible intervals (CrIs). We used a normal likelihood with an identity link for continuous outcomes (FEV1, TDI and SGRQ) and a binomial likelihood with a logit link for mortality, SAEs (total, cardiac and COPD), dropouts due to adverse events, SGRQ responders and pneumonia. We used a shared parameter model for exacerbation outcomes, whereby data on the log hazard ratio (lnHR and standard error) were modelled with the assumption that continuous treatment differences (lnHR) had a normal likelihood. When lnHR data were not available, or when appropriate covariance matrices could not be extracted or calculated for studies with more than two arms, we modelled data on the number of participants with at least one exacerbation out of the total number of participants at a given time as lnHR by using a binomial likelihood with Cloglog link. We used lnHR data in preference to dichotomous data when available and considered only the HR for the first event. We assessed model fit by comparing residual deviance to the number of data points, and by assessing the size of the between-study standard deviation (SD).

Direct pairwise meta-analysis

We conducted pairwise meta-analyses (MAs) considering only direct evidence. We analysed dichotomous data as ORs and continuous data as mean differences (MDs) along with their 95% confidence intervals (CIs). We undertook MAs only when this was meaningful (i.e. if treatments, participants and the underlying clinical question were similar enough for pooling to make sense). When a single study reported multiple study arms, we included only the relevant arms.

Unit of analysis issues

We analysed dichotomous data by using number of participants (rather than events), as the unit of analysis to avoid multiple counting of data from the same participant.

Dealing with missing data

We requested additional data from the responsible author of the included studies to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as an abstract only). When this was not possible, and when the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by performing a sensitivity analysis.

Assessment of heterogeneity

Assessment of similarity of participants, interventions and study methods

We assessed similarity of participants, interventions, potential effect modifiers and study methods in all studies and across pairwise comparisons to examine heterogeneity and inconsistency in the NMAs. The initial editorial review for study protocol had questioned the similarity of patient populations across clinical studies owing to the presence of potential effect modifiers. After a preliminary search of clinical studies and a review of inclusion/exclusion criteria, participant characteristics and study methods, we decided to divide the study populations into those with and without a history of COPD exacerbations within 12 months before study entry, which we viewed as a potential effect modifier (Table 1). This is consistent with the GOLD 2018 update, which recommends treatment options based on an exacerbation history.
We assessed if there was any difference in effect modifiers across the group pairwise comparisons especially when there was a discrepancy between the NMA and pairwise MA results and interpreted the results accordingly.

Assessment of heterogeneity and statistical consistency

We assessed heterogeneity by comparing the between-study SD to the size of relative treatment effects, on the log-scale for OR and HR. We assessed consistency by comparing the model fit and between-study heterogeneity from the NMA models versus those from an unrelated mean-effects (inconsistency) model (Dias 2013a; Dias 2013b). We used this to determine the presence and area of inconsistency. We also qualitatively compared the results from direct pairwise MA versus NMA estimates to check for broad agreement. If we identified substantial inconsistency, we explored factors, including participant and design characteristics that may have contributed to inconsistency (Table 2; Table 3; Table 4; Table 5; Table 6). For the pairwise MA, we tested heterogeneity among studies with I^2 statistics greater than 30%, indicating substantial heterogeneity (Higgins 2003). We used optimal information size calculations as an objective measure of imprecision for grading evidence, with an α of 0.05 and a β of 0.80 (Guyatt 2011a). We addressed heterogeneity in the pairwise MAs according to the GRADE criteria (Guyatt 2011b).

Assessment of reporting biases

We tried to minimise reporting biases from unpublished studies or selective outcome reporting by using a broad search strategy and by checking references of included studies and relevant systematic reviews. For each outcome, we reported the number of studies contributing data to the NMAs. For the pairwise MA, we assessed small study and publication bias through visual inspection of a funnel plot and performance of the Egger test (Egger 1997), if more than 10 studies were being pooled. We assumed the presence of small study bias when the number of participants was fewer than 50 per study, 1000 per pooled analysis or 100 per arm, when no more than 10 studies could be pooled (Dechartres 2013; Nüesch 2010). We assumed a selective reporting bias if a clinical study was not registered (Mathieu 2009).

Data synthesis

We based model comparison on deviance information criterion (DIC) (Spiegelhalter 2002). Differences of three points or more were considered meaningful. If models differed by less than three points, we selected the simplest model. We also calculated the posterior mean of the residual deviance to assess model fit. We considered this adequate when the posterior mean of the residual deviance approximated the number of unconstrained data points (Dias 2013c).

We chose a model and considered it as the primary analysis for NMAs using the following strategy:

1. Start with fixed-class models (random- and fixed-treatment-effects). If both fit well, choose model with lowest DIC (if difference less than 3 choose fixed-effect model) and stop.
2. If the fixed-treatment-effect, fixed-class model does not fit well, try the fixed-treatment-effect, random-class model - assess fit and choose the model with the lowest DIC.
3. If neither fixed- nor random-treatment-effect models with fixed-class fit well, try also random-treatment-effects with random-class.
4. Choose a final model based on DIC, but interpret with caution if model fit is poor.

We estimated the probability that each treatment group ranked at one of the four possible positions in the class model NMAs with rank 1 meaning that group is best for that outcome.

GRADE and 'Summary of findings' table

We used GRADE to assess the quality of evidence as it related to studies that contributed data to the pairwise MAs. We created a 'Summary of findings' table including the primary outcomes and pneumonia. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias), to assess the certainty of a body of evidence as it related to studies that contributed data to pairwise MAs for prespecified outcomes. We used methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017), and used GRADEpro GDT 2015 software. We justified all decisions to downgrade or upgrade the certainty of evidence by using footnotes, and we made comments to aid the reader's understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We combined the high- and low-risk populations (presence or absence of a history of COPD exacerbation within the previous year), and performed subgroup analyses investigating if there was a substantial difference between them. We analysed studies of different duration separately (3, 6, and 12 months), for symptom and quality-of-life scores and change from baseline in FEV1 to minimise intransitivity because a previous study (Oba 2016a), suggested different durations could influence treatment effects on these outcomes. We used a formal test for subgroup interactions provided in Review Manager 2014.

Sensitivity analysis

We used a model not used in the primary analysis (fixed-effect or random-effects), as a sensitivity analysis for both NMAs and pairwise MAs.

RESULTS

Description of studies

The study and patient characteristics including study duration, treatment arms, and baseline pulmonary function are presented in Table 1 and details of each study are shown in Characteristics of included studies.

Results of the search

We identified 870 plus 166 records (original and updated search respectively), from the Cochrane Airways Specialised Register (CAGR) of studies, and 28 references through other sources, such as manufactures' websites. We searched all records in the CAGR using the search strategy in Appendix 2 in March 2017 and again on 6 April 2018 for the updated search. We excluded 119 studies on abstract review. We reviewed the remaining 156 studies for further details and excluded an additional 57 studies for various reasons as shown in Figure 1.

Included studies

We included 26 studies with 32,265 participants in the high-risk group (one or more exacerbations in the previous 12 months), and 73 studies with 69,046 participants in the low-risk group, totaling 99 studies with a total of 101,311 randomised participants. The numbers of included studies varied with each outcome due to data availability and are summarised in Figure 1. Four in the low-risk group (Hoshino 2013; Hoshino 2014; Hoshino 2015; Perng 2009), and one in the high-risk group (Sarac 2016), were single-centre studies and the rest were multicenter studies. They were all industry-funded studies except for Aaron 2007, Cazzola 2007, Hoshino 2013, Hoshino 2014, Hoshino 2015, Perng 2009, and Sarac 2016.

Figure 1. Study flow diagram

AEs: adverse events; CAGR: Cochrane Airways Group Specialised Register; CFB: change from baseline; H: high−risk group; L: low−risk group; NA: not applicable; NMA: network meta−analysis; SAE: serious adverse event; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnea Index

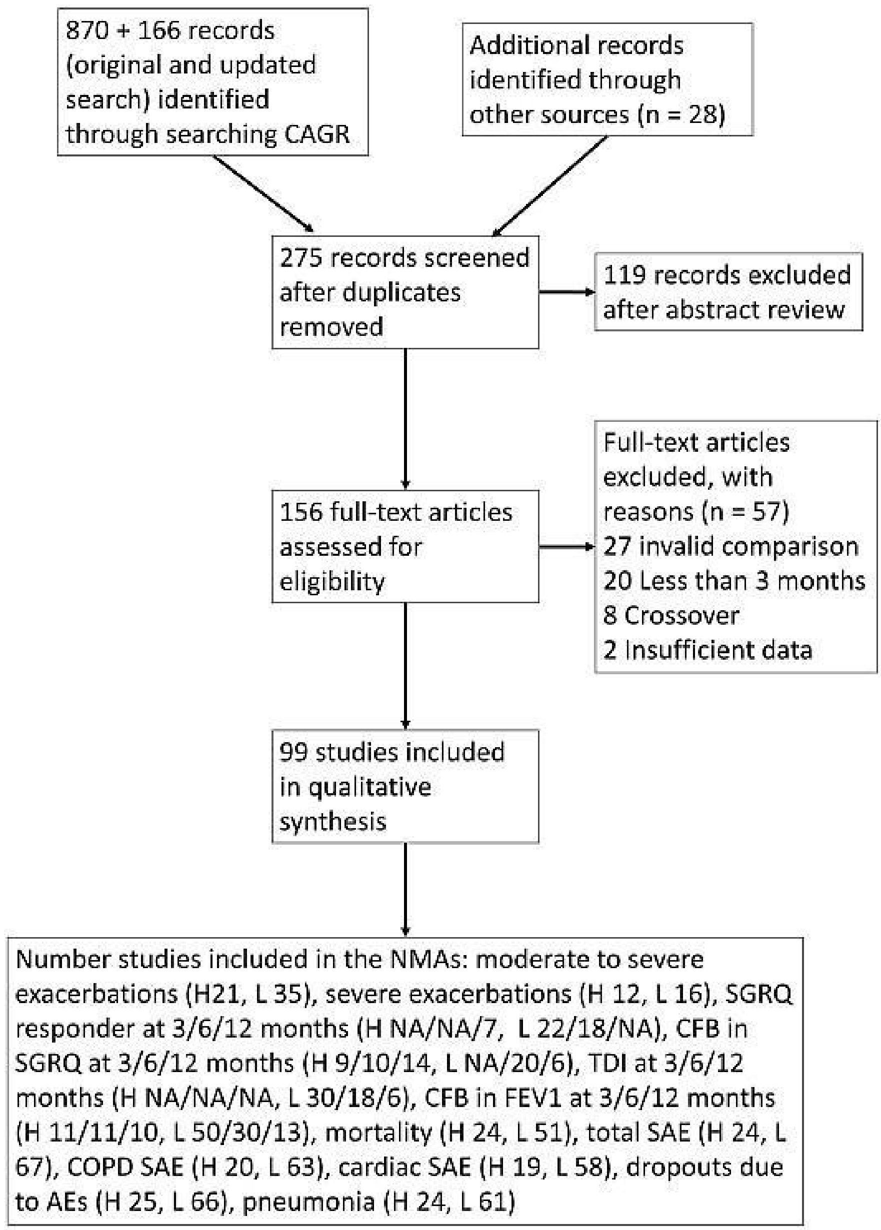


Table 2, Table 3, Table 4, Table 5, and Table 6 show comparisons of study characteristics among pairwise MAs in the relevant outcomes. The median duration of study was 52 (range 12 to 156) and 24 (range 12 to 156) weeks in the high- and low-risk groups respectively.

Table 7; and Table 8 present the distribution of treatment arms across all 99 included studies, categorised by the four treatment groups. Vilanterol is available only as a component of combination inhalers for clinical use (i.e. it is not available as a single inhaler), therefore we did not include vilanterol as a node in the review. Indacaterol 27.5 μg and 600 μg twice daily, indacaterol/glycopyrronium 27.5 μg/25 μg twice daily, umeclidinium/vilanterol 125 μg/25 μg once daily, tiotropium/olodaterol 2.5 μg/5 μg once daily, and aclidinium/formoterol 400 μg/6 μg twice daily were also excluded from the analysis because they were not approved or available for clinical use at the time of data extraction. The network of treatments for each outcome is displayed in a corresponding figure. The treatments formed a closed network, which was amenable to a NMA except for SGRQ responders at 3 and 6 months, and TDI at 3, 6, and 12 months in the high-risk population, and SGRQ responders at 12 months in the low-risk population. When fixed- or random-class models were considered, all networks were connected and could be analysed.

Participants

The mean age, proportion of male participants and current smokers, and pre-bronchodilator baseline FEV1, were 64.5 years (SD 1.5), 72.5% (SD 11.7), 39.0% (SD 6.0), and 1.06 L (SD 0.11), in the high-risk group and 64.6 years (SD 2.4), 72.5% (SD 12.3), 46.0% (SD 8.1), and 1.31 L (SD 0.13), in the low-risk group. The median bronchial reversibility at the baseline was 13.6% (range 7.0 to 22.4), and 14.2% (range 7.9 to 24.1), in the high- and low-risk groups respectively.

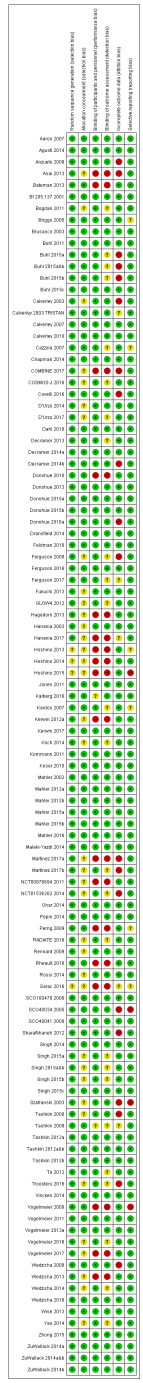
Excluded studies

We excluded 57 studies after full-text review and we recorded them in Characteristics of excluded studies, with reasons for exclusion. We excluded 27 studies because, after we had excluded an unapproved or unavailable dosage, there were no valid comparisons. Two studies became available after data extraction (Calverley 2018; Papi 2017), and we did not included them in the analysis. We would have excluded Calverley 2018 anyway because they included participants with coexisting reactive airway disease.

Risk of bias in included studies

We have presented 'Risk of bias' judgements for individual studies in the Characteristics of included studies and a summary overview of the findings in Figure 2. Generally, we deemed the risk of bias in the included studies to be moderate to low. There were no studies that we should clearly have excluded from the analysis because of differences in baseline characteristics or poor quality.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

All studies were randomised trials and most of them were industry funded. We confirmed a random allocation sequence using a validated computerised system in 60 out of 92 industry-funded studies, and assumed an industry-standard method for the rest and considered them to be at low risk for random sequence generation and allocation concealment (concealment assumed by automatisation). We could not confirm a random allocation sequence in four out of seven non-industry studies (Hoshino 2013; Hoshino 2014: Hoshino 2015: Sarac 2016), and we considered them to be at unclear risk.

Blinding

The following studies were open-label or partially blinded, with tiotropium being administered open-label, and considered to be at a high risk of bias: Asai 2013, Bateman 2013, COMBINE 2017, Donohue 2010, Hagedorn 2013, Hanania 2017, Hoshino 2013, Hoshino 2014, Hoshino 2015, Kerwin 2012a, Martinez 2017a, NCT00876694 2011, Perng 2009, Sarac 2016, Vogelmeier 2008, Vogelmeier 2017, Wedzicha 2013. They consisted of 15.4% and 17.8% of studies in the high- and low-risk populations. The rest of the studies were double-blinded (82.8%), and rated as having low risk of bias (blinding of participants, personnel and outcome assessors).

Incomplete outcome data

We rated 18 studies (18.1%), at high risk due to high attrition or unbalanced dropouts. We gave an unclear rating to four studies (4.0%), because of high but balanced attrition (Calverley 2003 TRISTAN), imbalanced but relatively low attrition (Ferguson 2017; Hanania 2017), and a small sample size with unknown attrition (Sarac 2016). We tested whether the above studies compromised the validity of the results by excluding them one by one or all together in each outcome. The results are described in 'Summary of findings' tables in the selected outcomes.

Selective reporting

We were able to locate a study protocol, and most studies reported confirmed expected outcomes in publications. We could not locate a preregistered protocol for five studies (Briggs 2005; Cazzola 2007: Hoshino 2013: Perng 2009: Sarac 2016), and rated them as unclear risk of bias. Two studies reported outcomes of interest but in an insufficient form to be incorporated into a meta-analysis and we rated them as having high risk of bias (Hoshino 2015; Vogelmeier 2008).

Other potential sources of bias

The vast majority of the included studies were designed, sponsored and conducted by pharmaceutical companies. Industry sponsorship bias cannot be excluded.

Effects of interventions

See: **Summary of findings for the main comparison** LABA/LAMA compared to LABA/ICS for chronic obstructive pulmonary disease; **Summary of findings 2** LABA/LAMA compared to LAMA for chronic obstructive pulmonary disease; **Summary of findings 3** LABA/LAMA compared to LABA for chronic obstructive pulmonary disease; **Summary of findings 4** LABA/ICS compared to LAMA for chronic obstructive pulmonary disease; **Summary of findings 5** LABA/ICS compared to LABA for chronic obstructive pulmonary disease; **Summary of findings 6** LAMA compared to LABA for chronic obstructive pulmonary disease; **Summary of findings 7** Summary of findings for network meta-analyses

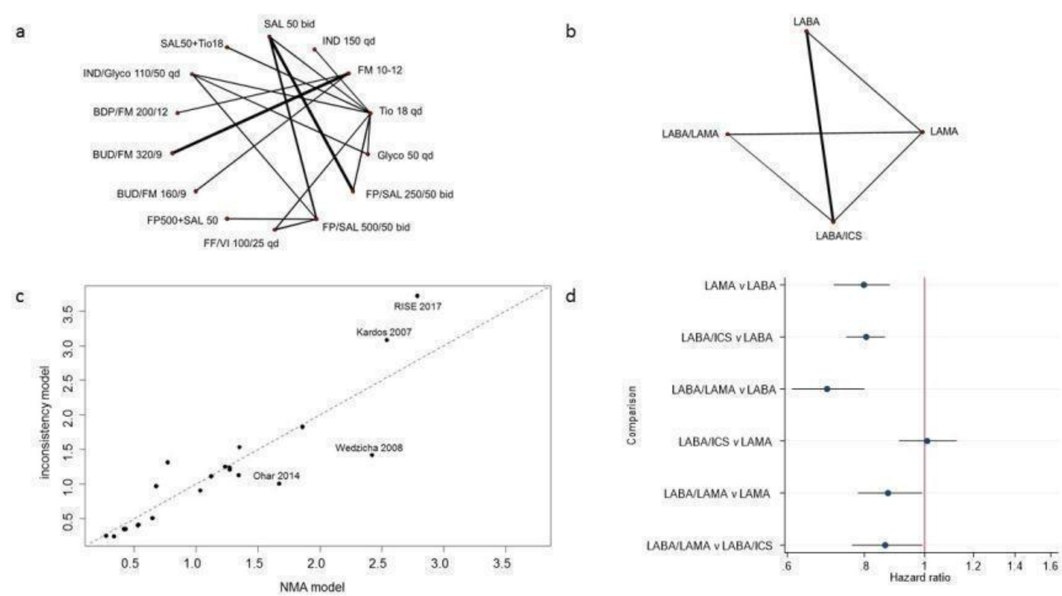
1. Results: high-risk population

1.1 Outcome: exacerbations

1.1.1 Outcome: moderate to severe exacerbations

We included 21 studies of 14 interventions and four treatment groups for this outcome (Appendix 3; Figure 3).

Figure 3. Moderate to severe exacerbations in the high-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 1 favour the first named treatment group. bid: twice daily; BDP: beclomethasone; BUD: budesonide; FF: fluticasone furoate; FM: formoterol; FP: fluticasone propionate; Glyco: glycopyrronium; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; qd: once daily; SAL: salmeterol; Tio: tiotropium; VI: vilanterol



1.1.1.1 Model selection and inconsistency checking

We chose a random-treatment-effects model with fixed-class effects, assuming consistency (Appendix 4).

1.1.1.2 NMA results

The NMA included a total of 25,771 participants (LABA: 10,279, LAMA: 6376, LABA/ICS: 8282, LABA/LAMA: 834). The median duration of follow-up was 52 weeks (range 12 to 156 weeks). Figure 3 and Table 9 show the HR for moderate to severe exacerbations for each group compared to every other. The NMA suggested that LABA/LAMA combination was the highest ranked treatment group to reduce moderate to severe exacerbations (95% CrI 1st to 2nd), followed by LAMA (95% CrI 2nd to 3rd), (Appendix 5; Table 10). HRs against LABA/ICS, LAMA, and LABA were 0.86 (95% CrI 0.76 to 0.99), 0.87 (95% CrI 0.78 to 0.99) and 0.70 (95% CrI 0.61 to 0.80), respectively (Appendix 6). LABA is the worst ranked treatment group for this outcome (95% CrI 4th to 4th), and all groups of interventions decrease the rate of moderate to severe exacerbations compared to LABA. HRs for other treatment groups versus LABA were 0.70 (95% CrI 0.61 to 0.80), 0.80 (95% CrI 0.75 to 0.86) and 0.80 (95% CrI 0.71 to 0.88) for LABA/LAMA, LABA/ICS, and LAMA respectively (Appendix 6; Summary of findings 7).

1.1.1.3 Clinical homogeneity assessment

Table 2 shows the clinical homogeneity assessment (or transitivity), across the available comparisons. Bronchial reversibility ranged from 7.0% to 18.3%. The mean bronchial reversibility for LABA/ICS versus LAMA comparison was 7%, which could have underestimated the effects of LABA/ICS. The NMA results should be interpreted with caution because of the difference in bronchial reversibility across the pairwise comparisons.

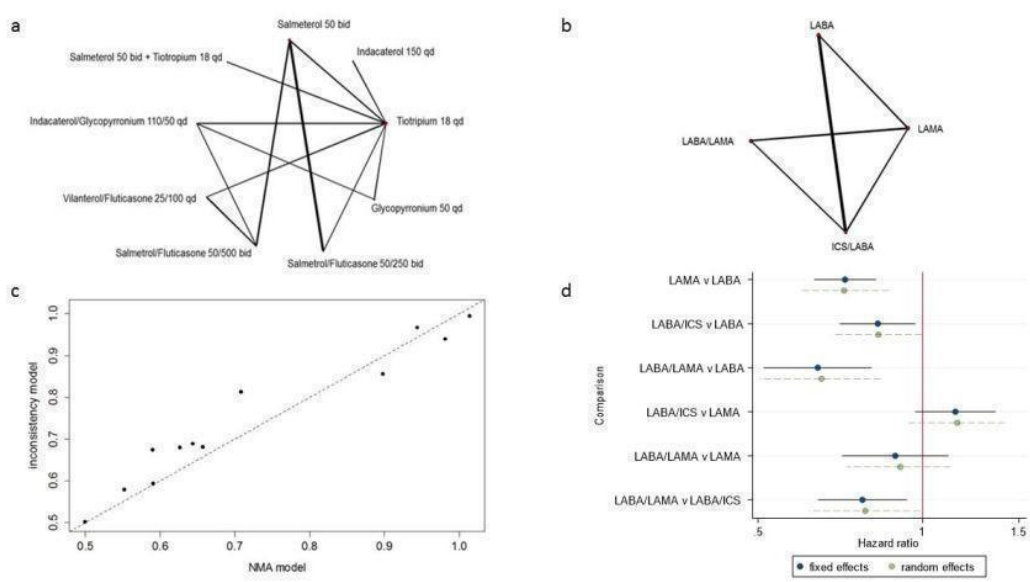
1.1.1.4 Pairwise meta-analyses

There was no direct comparison for LABA/LAMA versus LABA. The results from pairwise MAs were consistent with the NMAs except for LABA/LAMA versus LABA/ICS or LAMA, in which the 95% CI contained the line of no difference (OR 0.87, 95% CI 0.76 to 1.00, and OR 1.06, 95% CI 0.89 to 1.27), unlike the NMAs (HR 0.86, 95% CrI 0.76 to 0.99, and HR 0.87, 95% CrI 0.78 to 0.99; Appendix 6). The certainty of evidence was moderate for LABA/LAMA versus LABA/ICS or LAMA due to a suboptimal sample size, which could explain the discrepancy between the NMAs and pairwise MAs. Otherwise, it was moderate for LABA/ICS versus LAMA and high for LABA/ICS versus LABA and LAMA versus LABA (see 'Summary of findings' tables). There was no difference between random and fixed analyses.

1.1.2 Outcomes: severe exacerbations

We included 13 studies of nine interventions and four treatment groups for this outcome (Appendix 3; Figure 4 a and b).

Figure 4. Severe exacerbations in the high-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 1 favour the first named treatment group. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



1.1.2.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on a random-effects model for comparison (Appendix 4).

1.1.2.2 NMA results

This NMA included a total of 21,733 participants (LABA: 7482, LAMA: 7723, LABA/ICS: 4965, LABA/LAMA: 1563). The median duration of follow-up was 52 weeks (range 12 to 104 weeks). Figure 4 and Table 11 show the HR for severe exacerbations for each treatment group compared to every other. The NMA suggested that LABA/LAMA combination was the highest ranked treatment group to reduce severe exacerbations (95% CrI 1st to 2nd), followed by LAMA (95% CrI 1st to 3rd; Appendix 5; Table 12). HRs against LABA/ICS, LAMA, and LABA were 0.78 (95% CrI 0.64 to 0.93), 0.89 (95% CrI 0.71 to 1.11), and 0.64 (95% CrI 0.51to 0.81), respectively. Results using the fixed- or random-treatment-effects assumption are very similar. There is evidence that all treatment groups decrease the rate of severe exacerbations compared to LABA (HRs against LABA: 0.64 (95% CrI 0.51 to 0.81), 0.83 (95% CrI 0.71 to 0.97), and 0.72 (95% CrI 0.63 to 0.82), for LABA/LAMA, LABA/ICS and LAMA respectively), and that LABA/LAMA decreases the rate of severe exacerbations compared to LABA/ICS (HR 0.78, 95% CrI 0.64 to 0.93; Appendix 6; Summary of findings 7).

1.1.2.3 Clinical homogeneity assessment

Table 4 shows the clinical homogeneity assessment across the available comparisons. Bronchial reversibility ranged from 7.0% to 22.4% and was not available in three comparisons, which could have introduced a bias favouring an ICS-containing inhaler in a population with a significant bronchodilator response. The NMA results should be interpreted with caution because of the difference in and lack of data on bronchial reversibility.

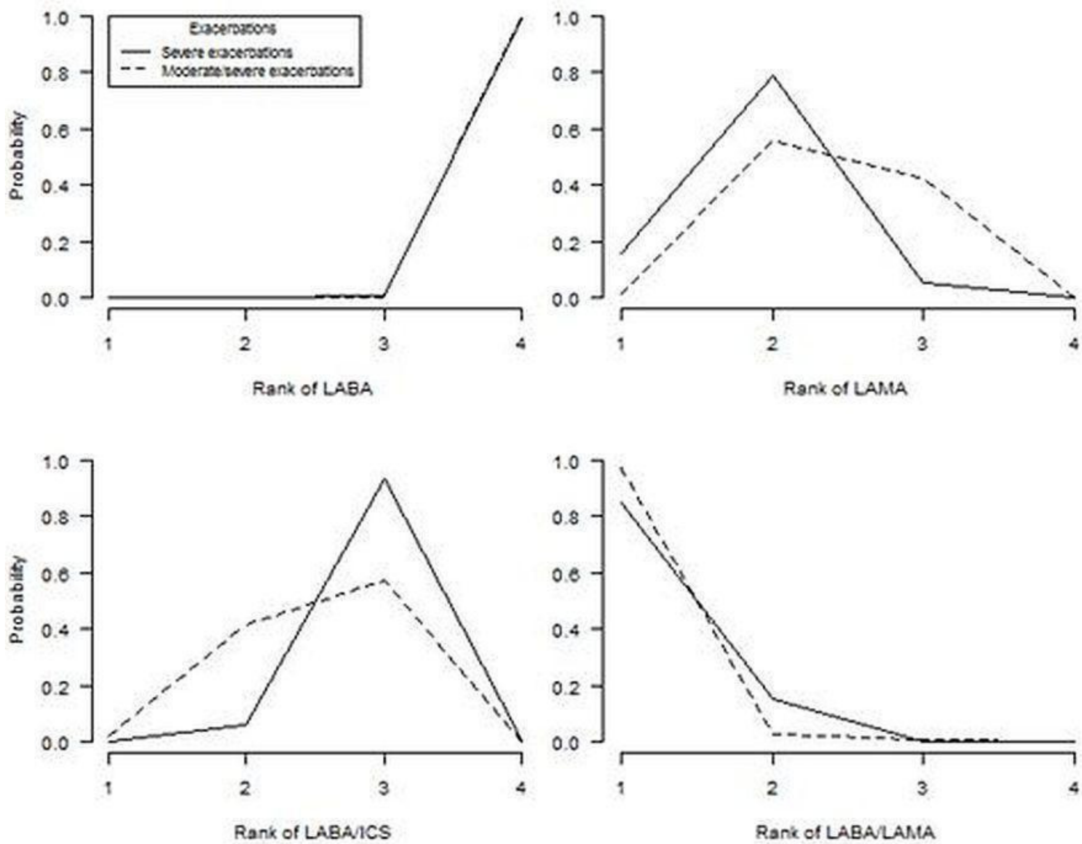
1.1.2.4 Pairwise meta-analyses

Contrary to the NMAs, the pairwise MAs showed no evidence that any treatment group was better than the others. There was no direct comparison for LABA/LAMA versus LABA (Appendix 6). The certainty of evidence was moderate for all comparisons due to a suboptimal information size, which could explain the discrepancy between the NMAs and pairwise MAs (See 'Summary of findings' tables). There was no difference between random and fixed analyses.

1.1.3 Rank probabilities for exacerbations

Figure 5 plots the ranks of each treatment group for severe exacerbations and moderate to severe exacerbations. The vertical axis shows the probability of being ranked best, second best, third best, or worst treatment group for each of the treatment groups. LABA/LAMA has a high probability of being the best intervention for both severe and moderate to severe exacerbations in the high-risk population, with a probability of nearly 100% of being the best treatment group to reduce moderate to severe exacerbations. LABA has a very high probability of being the worst treatment group for reducing both severe and moderate to severe exacerbations.

Figure 5. Plot of rank probabilities for each treatment group
Severe exacerbations (solid line), and moderate to severe exacerbations (dashed line), in the high-risk population ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



1.2 Outcome: St George's Respiratory Questionnaire (SGRQ) responders

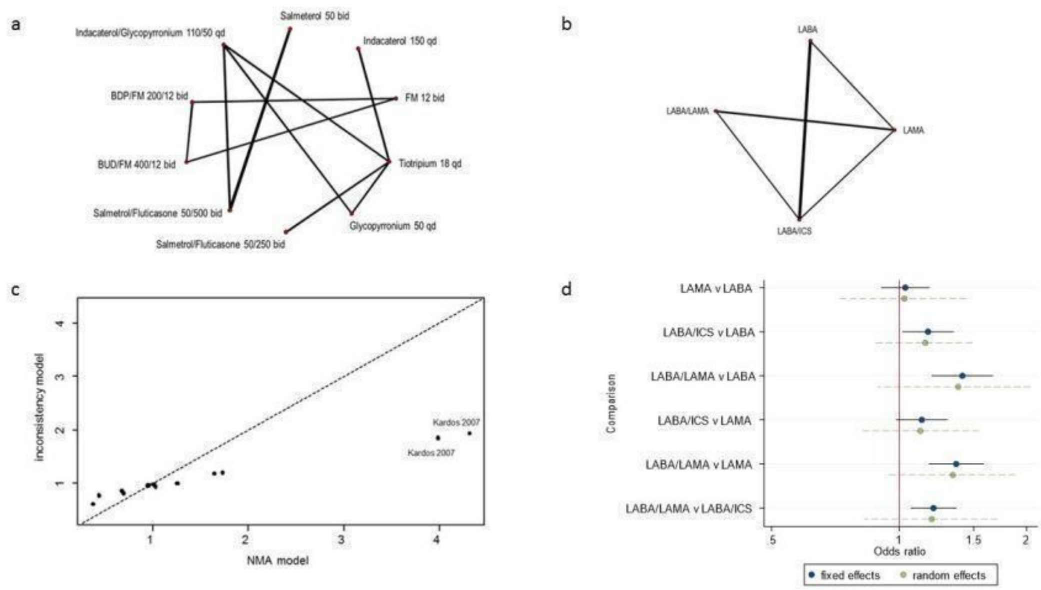
1.2.1 Outcome: SGRQ responders at three and six months

There were insufficient data to perform a NMA for SGRQ responders at three and six months. The results were based on one study for the following comparisons: LABA/LAMA versus LAMA at six months; LABA/ICS versus LAMA at three and six months; and LAMA versus LABA at three and six months. There is no evidence to suggest any treatment group is associated with a higher proportion of SGRQ responders compared to the others except for LABA/LAMA versus LAMA at six months, in which LABA/LAMA had a significantly greater proportion of SGRQ responders compared to LAMA (OR 1.30, 95% CI 1.08 to 1.56; Appendix 6). The certainty of evidence was low to moderate.

1.2.2 Outcome: SGRQ responders at 12 months

Seven studies of 10 interventions and four treatment groups were available for this outcome (Appendix 3; Figure 6 a and b). Note that interventions formoterol 12 μg twice daily, formoterol/budesonide 400μg/12 μg twice daily, and formoterol/beclomethasone 200 μg/12 μg twice daily are disconnected from the main treatment network (Figure 6a), but we included them in a class/group model.

Figure 6. St George's Respiratory Questionnaire responders at 12 months in the high-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 1 favour the first named treatment group. BDP: beclomethasone; BUD: budesonide; FM: formoterol; ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



1.2.2.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on a random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

1.2.2.2 NMA results

The NMA included a total of 11,089 participants (LABA: 2313, LAMA: 3078, LABA/ICS: 3496, LABA/LAMA: 2202). Figure 6d and Table 13 show the ORs of SGRQ responders at 12 months for each treatment group compared to every other. There is evidence to suggest that LABA/ICS increases the odds of response at 12 months compared to LABA (OR 1.17, 95% CrI 1.02 to 1.34), and that LABA/LAMA increases the odds of response compared to all other treatment groups (OR 1.21, 95% CrI 1.07 to 1.36; OR 1.36, 95% CrI 1.18 to 1.58, and OR 1.41, 95% CrI 1.20 to 1.66, against LABA/ICS, LAMA and LABA respectively), using the fixed-treatment-effect model. Results are more uncertain when random-treatment effects are assumed. Table 14 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group was LABA/LAMA with a median rank of 1 (95% CrI 1st to 1st).

1.2.2.3 Pairwise meta-analyses

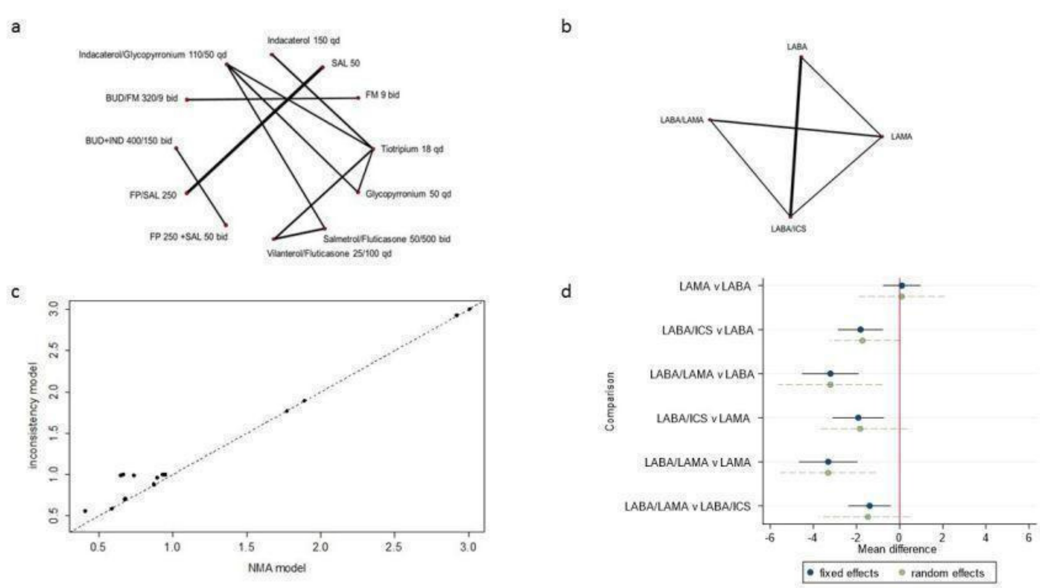
The results from pairwise MAs were consistent with the fixed-effect NMA except for LABA/ICS versus LABA, in which LABA/ICS significantly increased the odds of SGRQ response compared to LABA with the fixed-effect model (OR 1.22, 95% CI 1.03 to 1.46), but not with the random-effects model (OR 1.15, 95% CI 0.78 to 1.72). There was no direct comparison for LABA/LAMA versus LABA. The certainty of evidence was high for LABA/LAMA versus LABA/ICS, moderate for LABA/ICS versus LAMA or LABA and LAMA versus LABA, and low for LABA/LAMA versus LAMA. There was no difference between random and fixed analyses except for LABA/ICS versus LABA, in which the difference was significant with the fixed model but not with the random model (Appendix 6).

1.3 Change from baseline in SGRQ score

1.3.1 Outcome: change from baseline in SGRQ score at three months

We included nine studies of 12 interventions and four treatment groups for this outcome (Appendix 3; Figure 7 a and b). Note that interventions salmeterol 50 μg twice daily, formoterol 9 μg twice daily, salmeterol 50 μg twice daily + fluticasone 250 μg twice daily, salmeterol/fluticasone 50 μg/250 μg twice daily, indacaterol 150 μg once daily + budesonide 400 μg twice daily, and formoterol/budesonide 9 μg/320 μg twice daily are disconnected from the main treatment network (Figure 7a), but we included them in a class/group model.

Figure 7. Change from baseline in St George's Respiratory Questionnaire score at 3 months in the high-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 0 favour the first named treatment group. BUD: budesonide; FM: formoterol; FP: fluticasone propionate; ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; SAL: salmeterol



1.3.1.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on a random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

1.3.1.2 NMA results

The NMA included a total of 11,263 participants (LABA: 2764, LAMA: 2992, LABA/ICS: 3220, LABA/LAMA: 2287). Figure 7d and Table 15 show the mean difference in change from baseline in SGRQ score at three months for each treatment group compared to every other. There is evidence to suggest that both LABA/LAMA and LABA/ICS improve SGRQ score at three months compared to LABA (MD −3.21, 95% CrI −4.52 to −1.92; MD −1.82, 95% CrI −2.86 to −0.78), and LAMA monotherapies (MD −3.31, 95% CrI −4.67to −1.97; MD −1.92, 95% CrI −3.11 to −0.74) and that LABA/LAMA improves the score compared to LABA/ICS, when the fixed-treatment-effect model is used (MD −1.39, 95% CrI −2.37 to −0.42). The 95% CI exceeding minimal clinically important difference (MCID) of 4 suggests a possibility of clinically significant improvement favouring LABA/LAMA over LAMA and LABA. Results are more uncertain when considering the random-treatment-effects model although there is evidence that LABA/LAMA improves the score compare to LABA and LAMA monotherapies. Table 16 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group is LABA/LAMA with a median rank of 1 (95% CrI 1st to 1st).

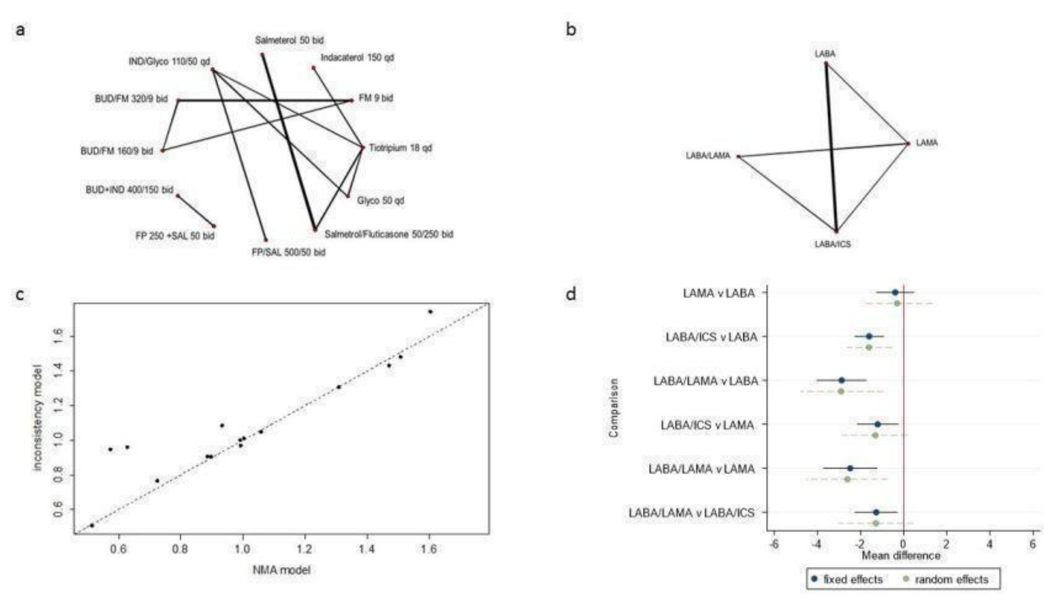
1.3.1.3 Pairwise meta-analyses

There was no direct comparison for LABA/LAMA versus LABA. Otherwise, the results from pairwise MAs were consistent with the NMAs, except for LABA/ICS versus LAMA, in which the 95% CI crossed the line of no difference with the pairwise MA (MD −1.06, 95% CI −4.39 to 2.27) and the random-effects NMA (MD −1.83, 95% CrI −3.76 to 0.35)) but not with the fixed-effect NMA (MD −1.92, 95% CrI −3.11 to −0.74; Appendix 6 and Table 15). The certainty of evidence for LAMA/ICS versus LAMA was low, as in the NMAs. A clinically important improvement cannot be excluded with LABA/LAMA compared to LAMA (MD −3.68, 95% CI −5.84 to −1.52), as well as with LABA/ICS compared to LAMA (MD −1.06, 95% CI −4.39 to 2.27), because the 95% CIs crossed the line of MCID of 4. Otherwise, there is no evidence of a clinically significant difference in treatment effects between treatment groups. The certainty of evidence was high for LABA/LAMA versus LABA/ICS and LAMA versus LABA, moderate for LABA/LAMA versus LAMA, and low for LABA/ICS versus LABA. There was no difference between random and fixed analyses.

1.3.2 Outcome: change from baseline in SGRQ score at six months

We included 10 studies of 12 interventions and four treatment groups for this outcome (Appendix 3, Figure 8 a and b). Note that interventions formoterol 9 μg twice daily, salmeterol 50 μg twice daily + fluticasone 250 μg twice daily, indacaterol 150 μg once daily + budesonide 400 μg twice daily, formoterol/budesonide 9 μg/160 μg twice daily and formoterol/budesonide 9 μg/320 μg twice daily are disconnected from the main treatment network (Figure 8a), but we included them in a class/group model.

Figure 8. Change from baseline in St George's Respiratory Questionnaire score at 6 months in the high-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 0 favour the first named treatment group. BUD: budesonide; FM: formoterol; FP: fluticasone propionate; Glyco: glycopyrronium; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; SAL: salmeterol



1.3.2.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on a random-treatment-effects model with fixed-class effects for comparison (Table 17).

1.3.2.2 NMA results

The NMA included a total of 12,967 participants (LABA: 3091, LAMA: 3273, LABA/ICS: 4317, LABA/LAMA: 2286). Figure 8d and Table 17 show the mean difference in change from baseline in SGRQ score at six months for each treatment group compared to every other. There is evidence to suggest that both LABA/LAMA and LABA/ICS improve SGRQ score at six months compared to LABA (MD −2.88, 95% CrI −4.03 to −1.73; MD −1.60, 95% CrI −2.27 to −0.93), and LAMA monotherapies (MD −2.48, 95% CrI −3.72 to −1.24), and that LABA/LAMA improves the score compared to LABA/ICS (MD −1.27, 95% CrI −2.26 to −0.29), using a fixed-treatment-effect model. The 95% CI exceeding MCID of 4 suggests a possibility of clinically significant improvement favouring LABA/LAMA over LABA. Results are more uncertain when considering the random-treatment-effects model although there is evidence that LABA/ICS and LABA/LAMA improve the score compare to LABA. Table 18 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group is LABA/LAMA with a median rank of 1 (95% CrI 1st to 1st).

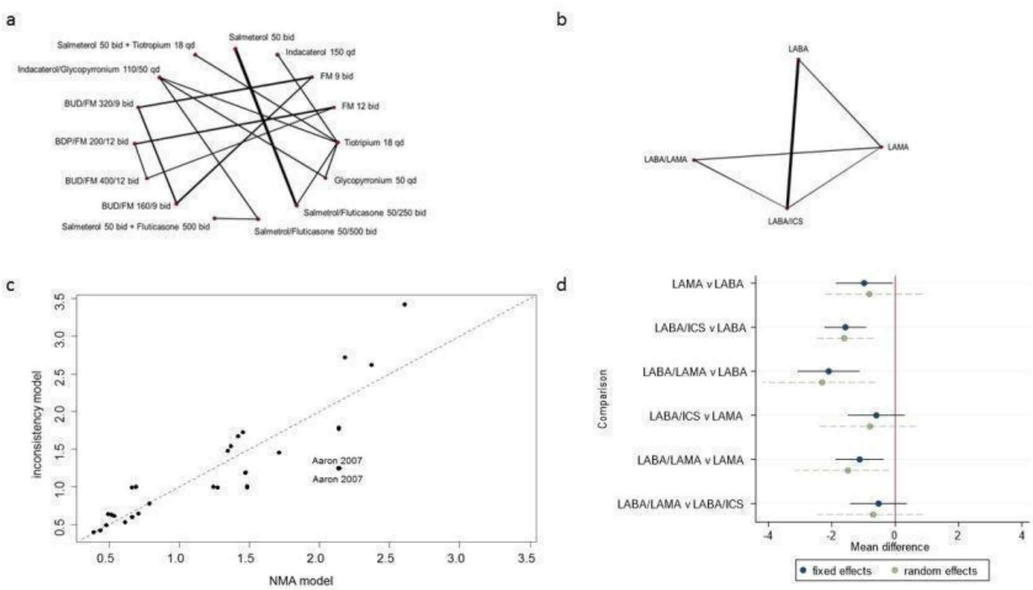
1.3.2.3 Pairwise meta-analyses

The results from pairwise MAs were consistent with the fixed-treatment-effect NMA. There was no direct comparison for LABA/LAMA versus LABA. A clinically important improvement could not be excluded with LABA/LAMA compared to LAMA because the 95% CIs crossed the line of MCID of 4 (MD −2.79, 95% CI −5.02 to −0.56). Otherwise, there is no evidence of a clinically significant difference in treatment effects between treatment groups although no clear difference was seen in the all comparisons except for LAMA versus LABA (MD −0.70, 95% CI −1.74 to 0.34; Appendix 6). The certainty of evidence was high for LABA/LAMA versus LABA/ICS and LAMA versus LABA, moderate for LABA/LAMA versus LAMA, low for LABA/ICS versus LAMA, and very low for LABA/ICS versus LABA. There was no difference between random and fixed analyses.

1.3.3 Outcome: change from baseline in SGRQ score at 12 months

We included 14 studies of 15 interventions and four treatment groups for this outcome (Appendix 3; Figure 9 a and b). Note that interventions formoterol 9 to 12 μg twice daily, formoterol/budesonide 9 μg/160 μg twice daily, formoterol/budesonide 12 μg/400 μg twice daily, formoterol/beclomethasone 12 μg/200 μg twice daily, and formoterol/budesonide 9 μg/320 μg twice daily are disconnected from the main treatment network (Figure 9a) but we included them in a class/group model.

Figure 9. Change from baseline in St George's Respiratory Questionnaire score at 12 months in the high-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 0 favour the first named treatment group. BDP: beclomethasone; BUD: budesonide; FM: formoterol; ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



1.3.3.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on a random-effects-model for comparison (Appendix 4).

1.3.3.2 NMA results

The NMA included a total of 15,459 participants (LABA: 4021, LAMA: 3216, LABA/ICS: 5891, LABA/LAMA: 2331). Figure 9d and Table 19 show the mean difference in change from baseline in SGRQ score at 12 months for each treatment group compared to every other. There is evidence to suggest that all treatment groups improve SGRQ score at 12 months compared to LABA (MD −2.10, 95% CrI −3.08 to −1.13; MD −1.57, 95% CrI −2.23 to −0.92; MD −0.98, 95% CrI −1.86 to −0.08 for LABA/LAMA, LABA/ICS and LAMA respectively), and that LABA/LAMA improves the score compared to LAMA (MD −1.12, 95% CrI −1.88 to −0.37), using the fixed-treatment-effect model. Results are more uncertain when considering the random-treatment-effects model although there is evidence that LABA/LAMA and LABA/ICS improve the score compared to LABA (MD −2.31, 95% CrI −4.17 to −0.64; MD −1.61, 95% CrI −2.52 to −0.69), and that LABA/LAMA improves the score compared to LAMA (MD −1.49, 95% CrI −3.16 to −0.20). The 95% CI exceeding MCID of 4 suggests a possibility of clinically significant improvement favouring LABA/LAMA over LABA. Table 20 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group is LABA/LAMA with a median rank of 1 (95% CrI 1st to 2nd).

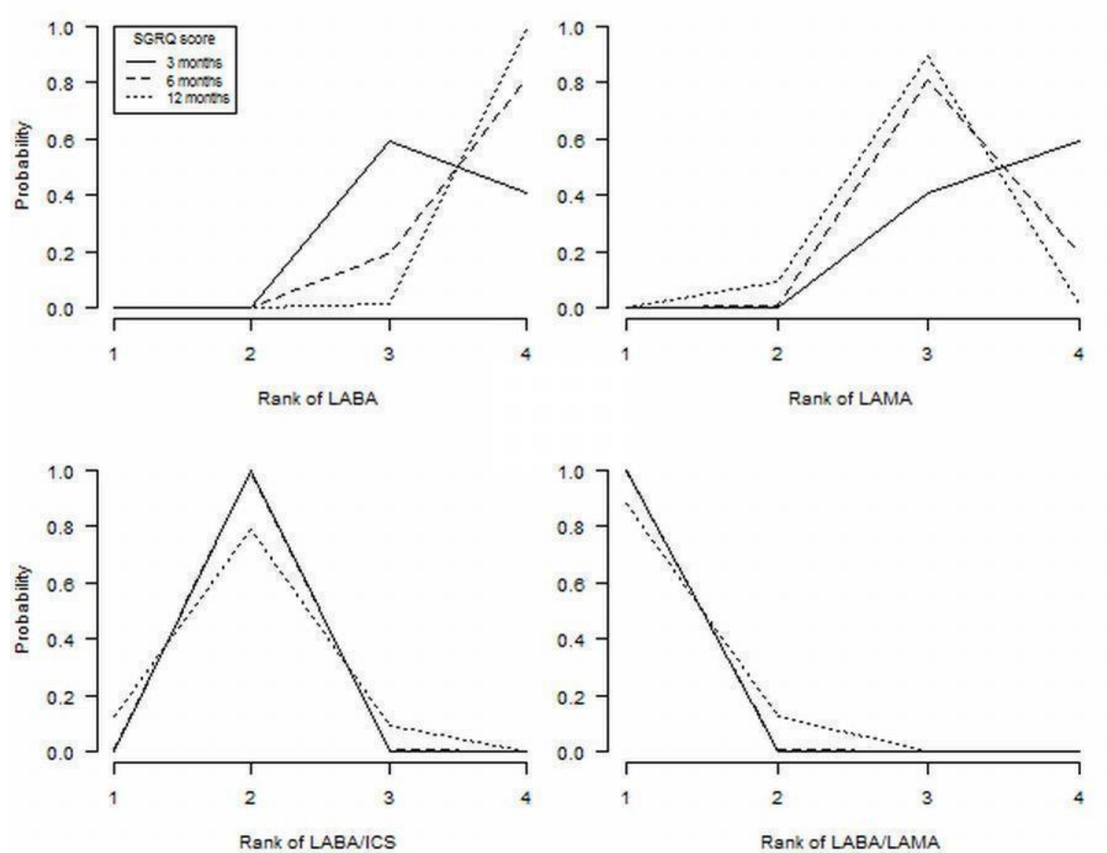
1.3.3.3 Pairwise meta-analyses

There is evidence to suggest that LABA/LAMA improves SGRQ score at 12 months compared to LABA/ICS or LAMA (MD −1.20, 95% CI −2.34 to −0.06 or MD −3.38, 95% CI −5.83 to −0.93), and that LABA/ICS improves the score compared to LABA (MD −1.75, 95% CI −2.61 to −0.89), although the mean differences do not reach the clinical significance of MCID of 4. There is no evidence of significant difference for LABA/ICS versus LAMA and LAMA versus LABA. There was no direct comparison for LABA/LAMA versus LABA. The results were consistent with the fixed-effect NMA except for LABA/LAMA versus LABA/ICS and LAMA versus LABA. LABA/LAMA significantly improved the score compared to LABA/ICS in the pairwise MA (MD −1.20, 95% CI −2.34 to −0.06), but not in the NMA (MD −0.52, 95% CrI −1.42 to 0.36), and LAMA improved the score compared to LABA in the NMA (MD −0.98, 95% CrI −1.86 to −0.08), but not in the pairwise MA (MD −0.40, 95% CI −1.56 to 0.76; Appendix 6). There is no evidence of clinically significant difference in any comparison except for LABA/LAMA versus LAMA, in which the 95% CI suggested a possibility of clinically significant improvement favouring LABA/LAMA over LAMA (MD −3.38, 95% CI −5.83 to −0.93). The certainty of evidence was high for LABA/LAMA versus LABA/ICS and LAMA versus LABA, moderate for LABA/ICS versus LABA, and low for LABA/LAMA or LABA/ICS versus LAMA. There was no difference between random and fixed analyses.

1.3.4 Rank probabilities for change from baseline in SGRQ score at 3, 6, and 12 months

Figure 10 plots the ranks of SGRQ score at 3, 6, and 12 months for each treatment group. The vertical axis shows the probability of being ranked best, second best, third best, or worst treatment group. LABA/LAMA has a high probability of being ranked first at every time point whereas LABA has a high probability of being ranked worst at 6 and 12 months.

Figure 10. Plot of rank probabilities for each treatment group
Change from baseline in St George's Respiratory Questionnaire score at 3 (solid line), 6 (dashed line), and 12 months (dotted line), in the high-risk population ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



1.4 Outcome: transition dyspnoea index (TDI)

1.4.1 TDI at 3, 6, and 12 months

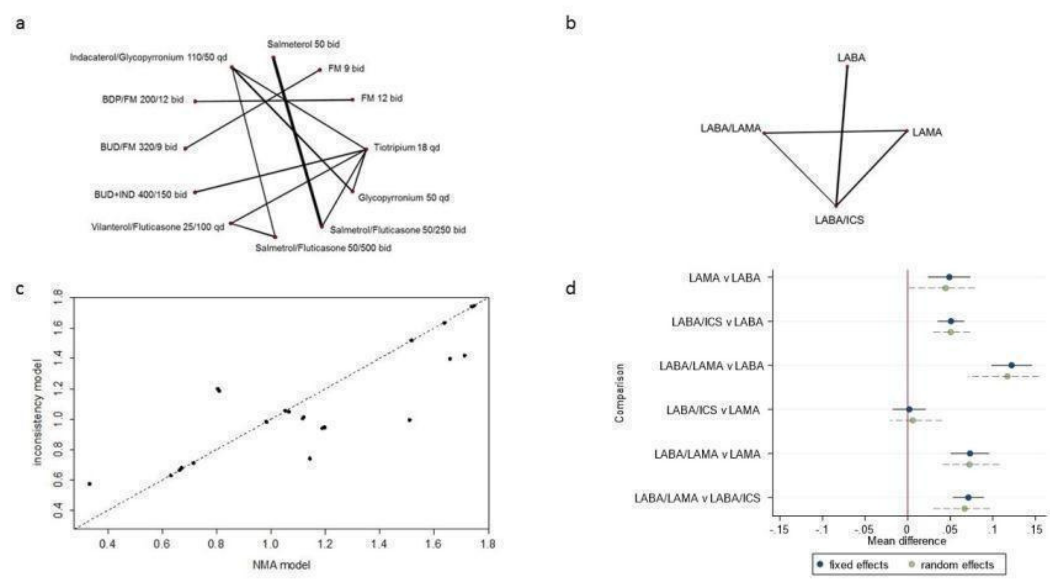
There were insufficient data to perform a NMA for TDI at 3, 6, and 12 months. The results were based on one trial for the following comparisons: LABA/ICS versus LAMA at 3, 6, and 12 months and LAMA versus LABA at 3, 6, and 12 months. There is no evidence of clinically significant improvement in TDI (MCID of 1), with any treatment group compared to the others although a significant difference was seen for LABA/ICS versus LAMA at three months (MD 0.50, 95% CI 0.18 to 0.82), and LAMA versus LABA at 3, 6, and 12 months (MD −0.14 95% CI −0.15 to −0.13; MD −0.19 95% CI −0.20 to −0.18; and MD −0.26 95% CI −0.27 to −0.25), favouring LABA/ICS over LAMA and LABA over LAMA (Appendix 6). The certainty of evidence was low for LABA/ICS versus LAMA at 12 months and moderate for the rest of the comparisons.

1.5 Outcome: change from baseline in forced expiratory volume in one second (FEV1)

1.5.1 Outcome: change from baseline in FEV1 at three months

We included 11 studies of 12 interventions and four treatment groups for this outcome (Appendix 3; Figure 11 a and b). Note that interventions formoterol 9 μg twice daily, formoterol 12 μg twice daily, formoterol/budesonide 9 μg/320 μg twice daily, and formoterol/beclomethasone 12 μg/200 μg twice daily are disconnected from the main treatment network (Figure 11a), but we included them in a class/group model.

Figure 11. Change from baseline in forced expiratory volume in 1 second at 3 months in the high-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Positive values favour the first named treatment group. BDP: beclomethasone; BUD: budesonide; FM: formoterol; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



1.5.1.1 Model selection and inconsistency checking

We chose a fixed-effect model with fixed-class effects, assuming consistency. We also report results based on a random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

1.5.1.2 NMA results

The NMA included a total of 11,668 participants (LABA: 2203, LAMA: 2010, LABA/ICS: 5192, LABA/LAMA: 2263). Figure 11d and Table 21 show the mean difference in change from baseline in FEV1 at three months for each treatment group compared to every other. There is evidence to suggest that all treatment groups improve FEV1 at three months compared to LABA (MD 0.12, 95% CrI 0.10 to 0.15; MD 0.05, 95% CrI 0.04, 0.07; and MD 0.05, 95% CrI 0.02 to 0.07 for LABA/LAMA, LABA/ICS, and LAMA respectively), and that LABA/LAMA improves FEV1 compared to LABA/ICS and LAMA (MD 0.07, 95% CrI 0.05 to 0.09; and MD 0.07, 95% CrI 0.05 to 0.10). The difference for LABA/LAMA versus LABA was of clinical significance favouring LABA/LAMA (MD 0.12, 95% CrI 0.10 to 0.15). The 95% CI reaching MCID of 0.1 L suggests a possibility of clinically significant improvement favouring LABA/LAMA over LAMA. Table 22 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group was LABA/LAMA with a median rank of 1 (95% CrI 1st to 1st), whereas LABA was the worst ranked with a median of 4 (95% CrI 4th to 4th).

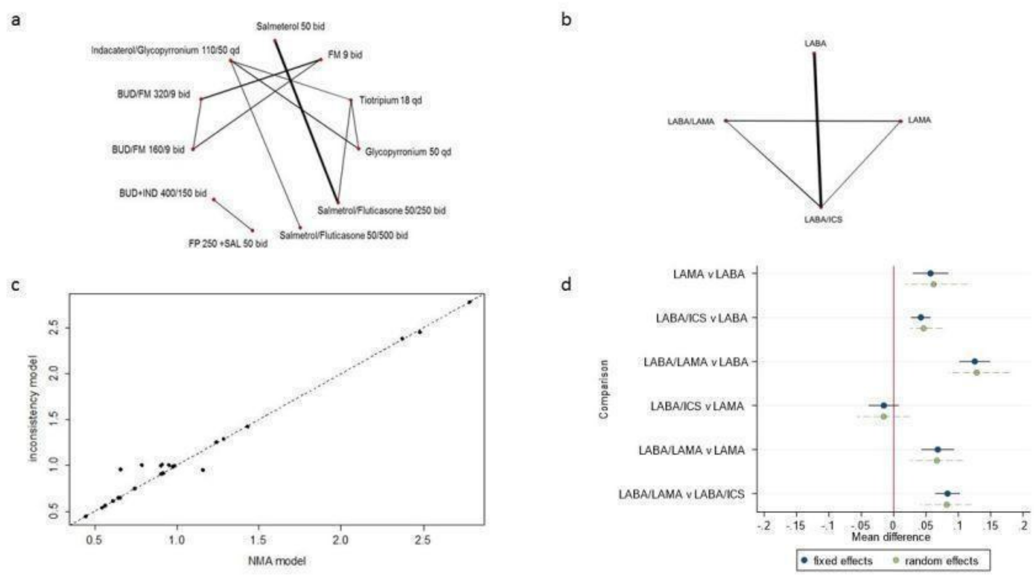
1.5.1.3 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs. There is no evidence of clinically significant improvement (MCID of 0.1 L or greater), with any treatment group compared to the others except for LABA/LAMA versus LABA/ICS, in which the 95% CI suggested a possibility of clinically significant difference favouring LABA/LAMA over LABA/ICS (MD 0.08, 95% CI 0.06 to 0.10; Appendix 6). There was no direct comparison for LABA/LAMA versus LABA and LAMA versus LABA. The certainty of evidence was high for LABA/LAMA versus LABA/ICS and LABA/ICS versus LAMA and moderate for LABA/LAMA versus LAMA and LABA/ICS versus LABA. There was no difference between random and fixed analyses.

1.5.2 Outcome: change from baseline in FEV1 at six months

Eleven studies of 11 interventions and four treatment groups were available for this outcome (Appendix 3; Figure 12 a and b). Note that interventions formoterol 9 μg twice daily, salmeterol 50 μg twice daily + fluticasone 250 μg twice daily, indacaterol 150 μg once daily + budesonide 400 μg twice daily, formoterol/budesonide 9 μg/160 μg twice daily, and formoterol/budesonide 9 μg/320 μg twice daily are disconnected from the main treatment network (Figure 12a), but we included them were in a class/group model.

Figure 12. Change from baseline in forced expiratory volume in 1 second at 6 months in the high-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Positive values favour the first named treatment group. BDP: beclomethasone; BUD: budesonide; FM: formoterol; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; SAL: salmeterol



1.5.2.1 Model selection and inconsistency checking

We chose a fixed-effect model with fixed-class effects, assuming consistency. We also report results based on a random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

1.5.2.2 NMA results

The NMA included a total of 10,822 participants (LABA: 2111, LAMA: 1700, LABA/ICS: 4263, LABA/LAMA: 2748). Figure 12d and Table 23 show the mean difference in change from baseline in FEV1 at six months for each treatment group compared to every other. There is evidence to suggest that all treatment groups improve FEV1 at six months compared to LABA, (MD 0.13, 95% CrI 0.10 to 0.15; MD 0.04, 95% CrI 0.03 to 0.06; and MD 0.06, 95% CrI 0.03 to 0.08 for LABA/LAMA, LABA/ICS, and LAMA respectively), and that LABA/LAMA improves FEV1 compared to LABA/ICS and LAMA (MD 0.08, 95% CrI 0.06 to 0.10; and MD 0.07, 95% CrI 0.04 to 0.09). The difference was clinically significant (MCID of 0.1 L or greater), for LABA/LAMA versus LABA (MD 0.13, 95% CrI 0.10 to 0.15), favouring LABA/LAMA over LABA with the fixed-effect model. The 95% CI reaching MCID of 0.1 L suggests a possibility of clinically significant improvement favouring LABA/LAMA over LABA/ICS. Table 24 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group is LABA/LAMA with a median rank of 1 (95% CrI 1st to 1st), whereas LABA was the worst ranked with a median of 4 (95% CrI 4th to 4th).

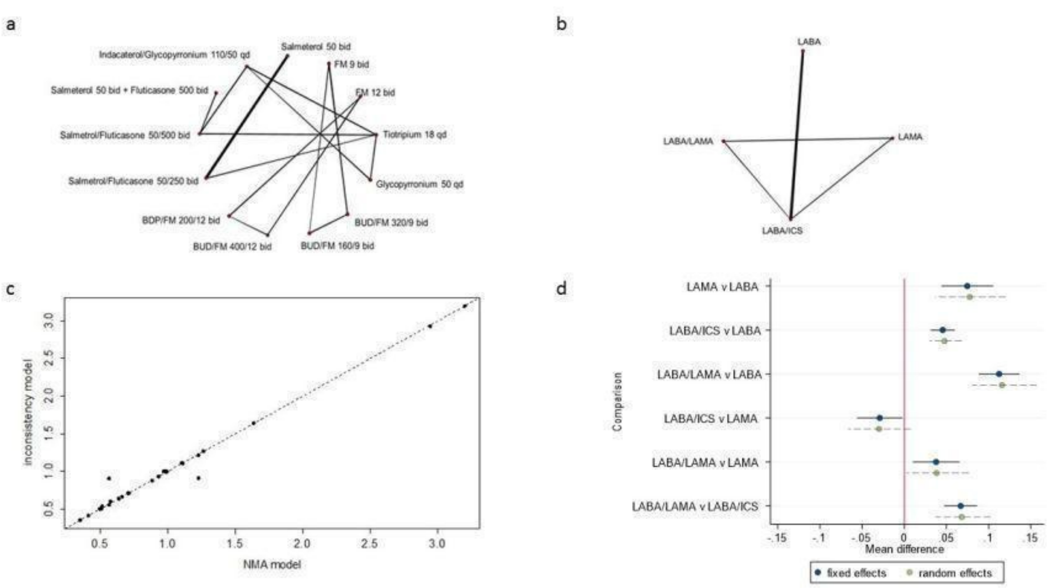
1.5.2.3 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs. There is no evidence of clinically significant improvement (MCID of 0.1 L or greater), with any treatment group compared to the others except for LABA/LAMA versus LABA/ICS or LAMA, in which the 95% CI suggested a possibility of clinically significant difference favouring LABA/LAMA over LABA/ICS or LAMA (MD 0.09, 95% CI 0.07 to 0.11; or MD 0.06, 95% CI 0.02 to 0.10; Appendix 6). There was no direct comparison for LABA/LAMA versus LABA and LAMA versus LABA. The certainty of evidence was high for LABA/LAMA versus LABA/ICS and moderate for LABA/LAMA versus LAMA and LABA/ICS versus LAMA or LABA. There was no difference between random and fixed analyses.

1.5.3 Outcome: change from baseline in FEV1 at 12 months

We included 13 studies of 13 interventions and four treatment groups for this outcome (Appendix 3; Figure 13a and b). Note that interventions formoterol 9 μg twice daily, formoterol 12 μg twice daily, formoterol/budesonide 9 μg/160 μg twice daily, formoterol/budesonide 12 μg/400 μg twice daily, and formoterol/beclomethasone 12 μg/200 μg twice daily are disconnected from the main treatment network (Figure 13a), but we included them in a class/group model.

Figure 13. Change from baseline in forced expiratory volume in 1 second at 12 months in the high-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Positive values favour the first named treatment group. BDP: beclomethasone; BUD: budesonide; FM: formoterol; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



1.5.3.1 Model selection and inconsistency checking

We chose a fixed-effect model with fixed-class effects, assuming consistency. We also report results based on a random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

1.5.3.2 NMA results

The NMA included a total of 11,171 participants (LABA: 1944, LAMA: 1919, LABA/ICS: 4982, LABA/LAMA: 2326). Figure 13d and Table 25 show the mean difference in change from baseline in FEV1 at 12 months for each treatment group compared to every other. There is evidence to suggest that all treatment groups improve FEV1 at 12 months compared to LABA (MD 0.12, 95% CrI 0.08 to 0.16; MD 0.05, 95% CrI 0.03 to 0.07; and MD 0.08, 95% CrI 0.04 to 0.12 for LABA/LAMA, LABA/ICS, and LAMA respectively), and that LABA/LAMA improves FEV1 compared to LABA/ICS (MD 0.07, 95% CrI 0.04 to 0.1). The 95% CI containing MCID of 0.1 L suggests a possibility of clinically significant improvement favouring LABA/LAMA over LABA/ICS and LABA and favouring LAMA over LABA. Table 26 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group is LABA/LAMA with a median rank of 1 (95% CrI 1st to 1st), whereas LABA was the worst ranked with a median of 4 (95% CrI 4th to 4th).

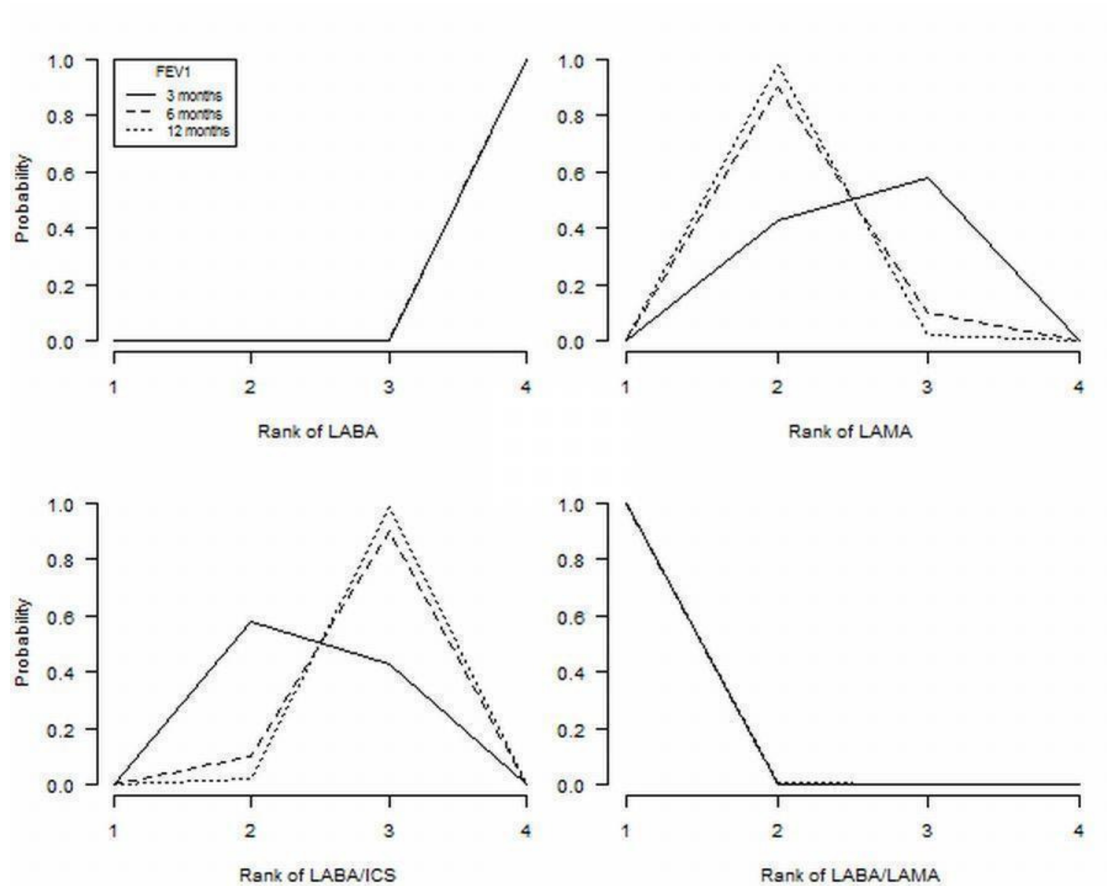
1.5.3.3 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs except for LABA/LAMA versus LAMA, in which there is evidence of significant improvement favouring LABA/LAMA over LAMA (MD 0.05, 95% CI 0.01 to 0.09). There was no direct comparison for LABA/LAMA versus LABA and LAMA versus LABA. Otherwise there is no evidence of clinically significant improvement (MCID of 0.1 L) with any treatment group compared to the others (Appendix 6). The certainty of evidence was very low for LABA/ICS versus LAMA and moderate for the rest of the available comparisons. There was no difference between random and fixed analyses.

1.5.4 Rank probabilities for change from baseline in FEV1 at 3, 6, and 12 months

Figure 14 plots the ranks of each treatment group for FEV1 at 3, 6 and 12 months. The vertical axis shows the probability of being the best, second best, third best, or worst treatment group. LABA/LAMA has nearly 100% probability of being ranked first at all time points with LABA having a very high probability of being the worst intervention at all time points.

Figure 14. Plot of rank probabilities for each treatment group
Change from baseline in forced expiratory volume in 1 second at 3 (solid line), 6 months (dashed line) and 12 months in the high-risk population. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist

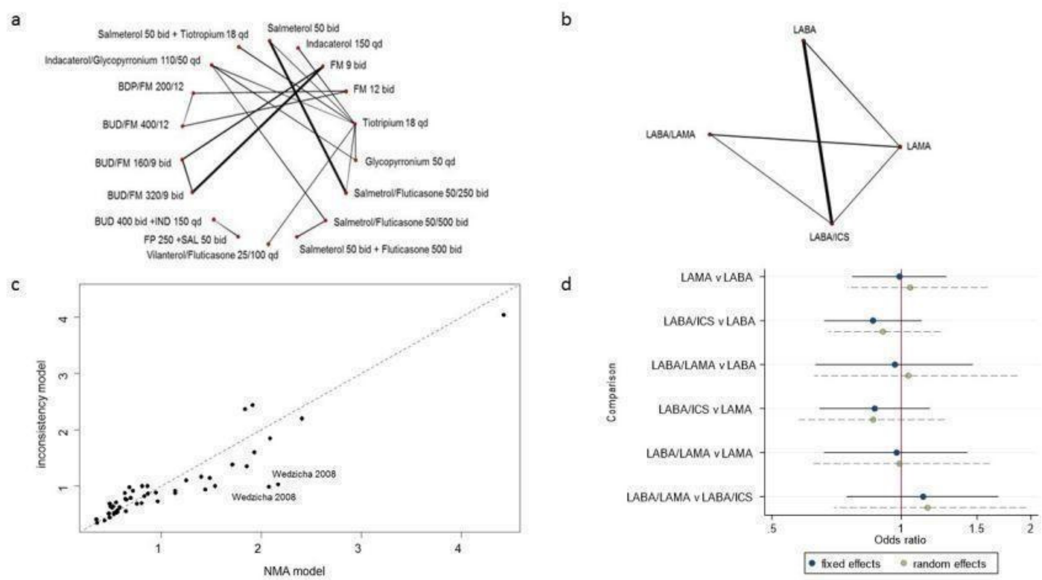


1.6 Outcome: mortality

Twenty-four studies of 18 interventions and four treatment groups were available for this outcome (Appendix 3; Figure 15 a and b). Note that interventions formoterol 9 μg twice daily, formoterol 12 μg twice daily, salmeterol 50 μg twice daily + fluticasone 250 μg twice daily, indacaterol 150 μg once daily + budesonide 400 μg twice daily, formoterol/budesonide 9 μg/160 μg twice daily, formoterol/budesonide 9 μg/320 μg twice daily, formoterol/budesonide 12 μg/400 μg twice daily, and formoterol/beclomethasone 12 μg/200 μg twice daily are disconnected from the main treatment network (Figure 15a), but we included them in a class/group model.

Figure 15. Mortality in the high-risk population

a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 1 favour the first named treatment group. BDP: beclomethasone; BUD: budesonide; FM: formoterol; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; SAL: salmeterol



1.6.1 Model selection and inconsistency checking

We chose a fixed-effect model with fixed-class effects, assuming consistency, although results should be interpreted with caution due to some evidence of inconsistency. We also report results based on a random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

1.6.2 NMA results

The NMA included a total of 31,674 participants (LABA: 11,182, LAMA: 7853, LABA/ICS: 10,084, LABA/LAMA: 2555). The median duration of follow-up was 52 weeks (range 12 to 156 weeks). Figure 15d and Table 27 show the OR of mortality for each treatment group compared to every other. There was no evidence to suggest that any treatment group increased or decreased the odds of mortality compared to any other. Table 28 shows the rank statistics for the four treatment groups (sorted by mean rank). All treatment groups have high uncertainty in ranks as expected, due to no treatment effect being identified for any treatment group.

1.6.3 Pairwise meta-analyses

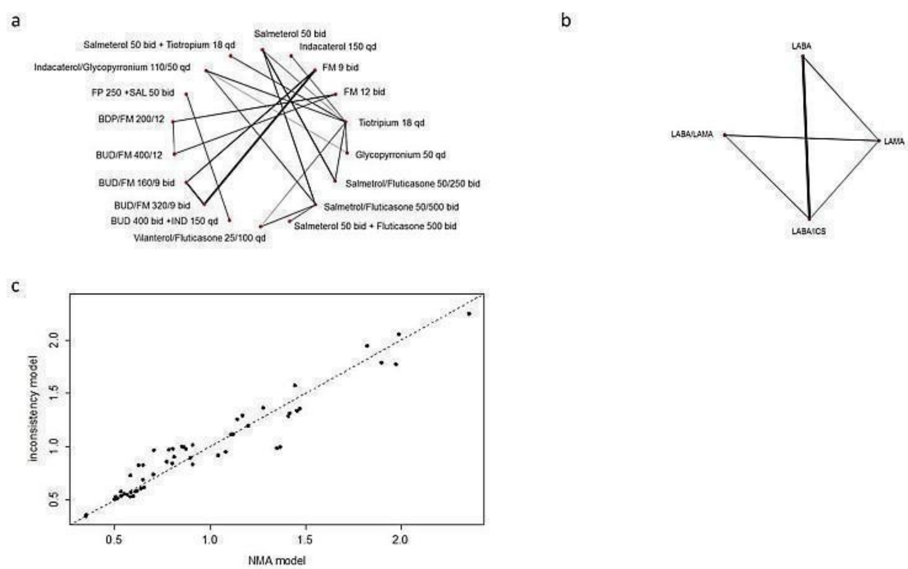
The results from pairwise MAs were consistent with the NMAs. There was no direct comparison for LABA/LAMA versus LABA (Appendix 6). The certainty of evidence was low for LABA/ICS versus LABA and moderate for the rest of available comparisons. There was no difference between random and fixed analyses.

1.7 Outcome: serious adverse events (SAEs)

1.7.1 Outcome: total SAEs

The analysis for total SAEs included 24 studies of 18 interventions and four treatment groups. We included a total of 31,721 participants (LABA: 10,942, LAMA: 7853, LABA/ICS: 10,371, LABA/LAMA: 2555; Appendix 3; Figure 16 a and b). The median duration of follow-up was 52 weeks (range 12 to 156 weeks). Note that interventions formoterol 9 μg twice daily, formoterol 12 μg twice daily, indacaterol 150 μg once daily + budesonide 400 μg twice daily, formoterol/budesonide 9 μg/320 μg twice daily, formoterol/budesonide 9 μg/160 μg twice daily, formoterol/budesonide 12 μg/400 μg twice daily, formoterol/beclomethasone 12 μg/200 μg twice daily and salmeterol 50 μg twice daily + fluticasone 250 μg twice daily are disconnected from the main treatment network (Figure 16a), but we included them in a class/group model.

Figure 16. Total serious adverse events in the high-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. BDP: beclomethasone; BUD: budesonide; FM: formoterol; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; SAL: salmeterol



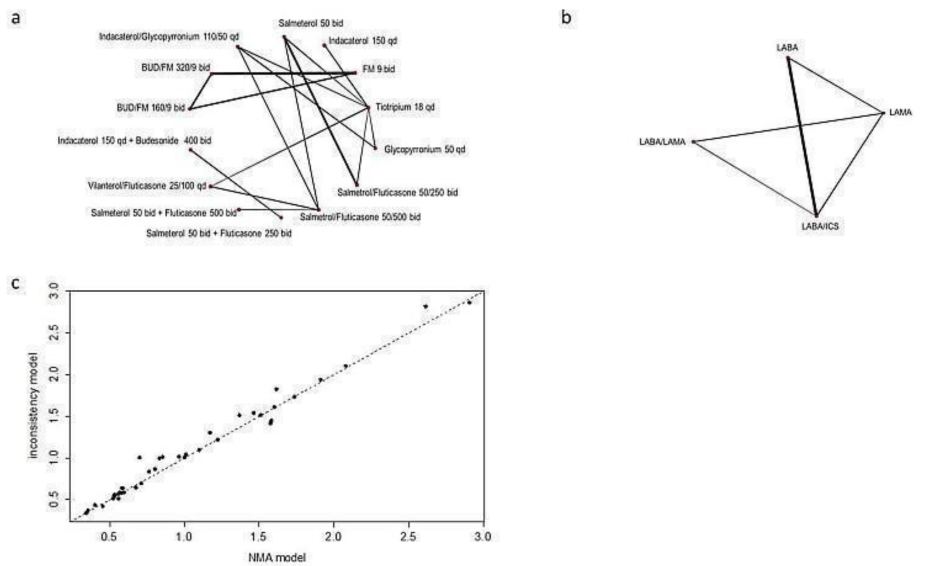
1.7.1.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on a random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

1.7.2 Outcome: chronic obstructive pulmonary disease (COPD) SAEs

The analysis for COPD SAEs included 20 studies of 14 interventions and four treatment groups. We included a total of 28,614 participants (LABA: 9675, LAMA: 7697, LABA/ICS: 8835, LABA/LAMA: 2407; Appendix 3; Figure 17 a and b). The median duration of follow-up was 52 weeks (range 12 to 156 weeks). Note that interventions formoterol 9 μg twice daily, salmeterol 50 μg twice daily + fluticasone 250 μg twice daily, indacaterol 150 μg once daily + budesonide 400 μg twice daily, formoterol/budesonide 9 μg/160 μg twice daily and formoterol/budesonide 9 μg/320 μg twice daily are disconnected from the main treatment network (Figure 17a), but we included them in a class/group model.

Figure 17. Chronic obstructive pulmonary disease serious adverse events in the high-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. BUD: budesonide; FM: formoterol; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



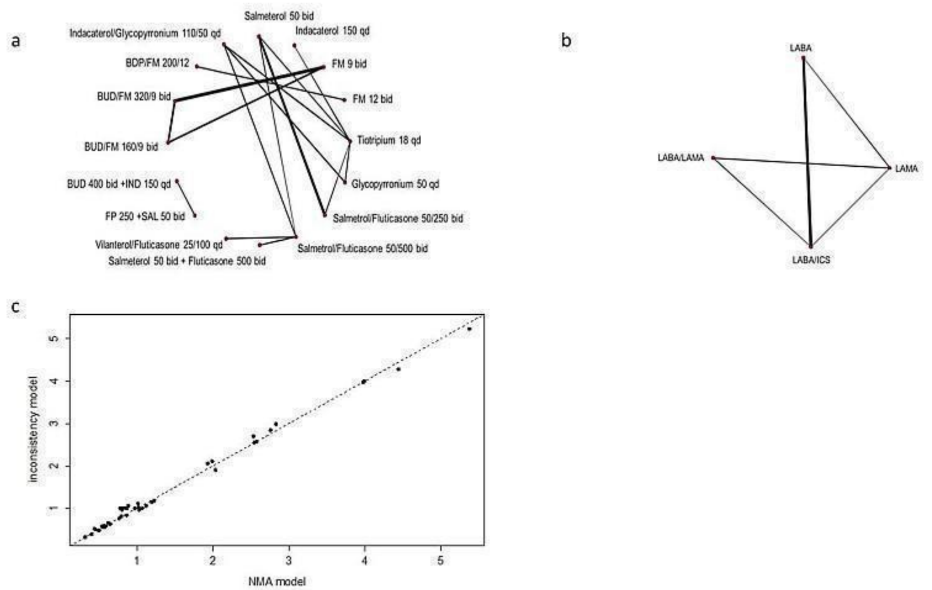
1.7.2.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on the random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

1.7.3 Outcome: cardiac SAEs

The analysis for cardiac SAEs included 19 studies of 16 interventions and four treatment groups (Appendix 3; Figure 18 a and b). We included a total of 29,045 participants (LABA: 10,016, LAMA: 7567, LABA/ICS: 9055, LABA/LAMA: 2407). The median duration of follow-up was 52 weeks (range 12 to 156 weeks). Note that interventions formoterol 9 μg twice daily, formoterol 12 μg twice daily, salmeterol 50 μg twice daily + fluticasone 250 μg twice daily, indacaterol 150 μg once daily + budesonide 400 μg twice daily, formoterol/budesonide 9 μg/160 μg twice daily, formoterol/budesonide 9 μg/320 μg twice daily, and formoterol/beclomethasone 12 μg/200 μg twice daily are disconnected from the main treatment network (Figure 18a), but we included them in a class/group model.

Figure 18. Cardiac serious adverse events in the high-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects BDP: beclomethasone; BUD: budesonide; FM: formoterol; FP: fluticasone propionate; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; SAL: salmeterol



1.7.3.1 Model selection and inconsistency checking

We chose a random-treatment-effects model with fixed-class effects, assuming consistency. We also report results based on the fixed-treatment-effect model with fixed-class effects for comparison (Appendix 4).

1.7.4 NMA results

Table 29 shows the OR of each type of adverse event for each treatment group compared to every other. For total SAEs there is evidence to suggest that LABA/ICS increases the odds of SAEs compared to LAMA (OR 1.14, 95% CrI 1.02 to 1.27), and that LAMA decreases the odds of SAEs compared to LABA (OR 0.88, 95% CrI 0.81 to 0.97), although this effect was only seen in the fixed-effect model. For COPD SAEs there is evidence to suggest that LABA/ICS increases the odds of SAEs compared to LAMA (OR 1.22 95% CrI 1.05 to 1.42), and that LAMA decreases the odds of SAEs compared to LABA (OR 0.77, 95% CrI 0.68 to 0.87), and this was seen in both models. No difference between treatment groups was evident for cardiac SAEs.

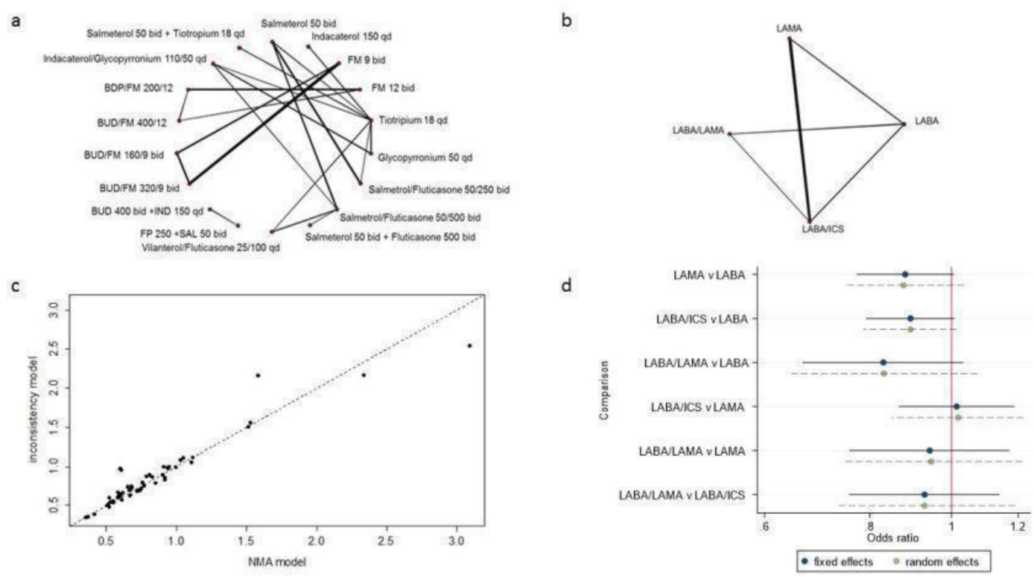
1.7.5 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs except for LABA/ICS versus LAMA for COPD SAEs in which the NMA suggested LABA/ICS increased the odds of COPD SAEs compared to LAMA (OR 1.22, 95% CrI 1.05 to 1.42), whereas the pairwise MA did not (OR 0.99, 95% CI 0.33 to 2.96). There was no direct comparison for LABA/LAMA versus LABA for total, COPD, and cardiac SAEs. Table 30 shows the certainty of evidence for each treatment group compared to every other. There was no difference between random and fixed analyses (Appendix 6).

1.8 Outcome: dropouts due to adverse events

We included 25 studies of 18 interventions and four treatment groups for this outcome (Appendix 3; Figure 19 a and b). Note that interventions formoterol 9 μg twice daily, formoterol 12 μg twice daily, salmeterol 50 μg twice daily + fluticasone 250 μg twice daily, indacaterol 150 μg once daily + budesonide 400 μg twice daily, formoterol/budesonide 9 μg/320 μg twice daily, formoterol/budesonide 9 μg/160 μg twice daily, formoterol/budesonide 12 μg/400 μg twice daily, and formoterol/beclomethasone 12 μg/200 μg twice daily are disconnected from the main treatment network (Figure 19a), but we included them in a class/group model.

Figure 19. Dropouts due to adverse events in the high-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 1 favour the first named treatment group. BDP: beclomethasone; BUD: budesonide; FM: formoterol; FP: fluticasone propionate; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; SAL: salmeterol



1.8.1 Model selection and inconsistency checking

We chose a fixed-effect model with fixed-class effects, assuming consistency. We also report results based on a random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

1.8.2 NMA results

The NMA included a total of 32,230 participants (LABA: 11,197, LAMA: 7853, LABA/ICS: 10,625, LABA/LAMA: 2555). The median duration of follow-up was 52 weeks (range 12 to 156 weeks). Figure 19d and Table 31 show the OR of dropout due to adverse events for each treatment group compared to every other. There was no evidence to suggest that any treatment group increased or decreased the odds of dropout compared to any other. Table 32 shows the rank statistics for the four treatment groups (sorted by mean rank). All treatment groups have high uncertainty in ranks as expected, due to no treatment effect being identified for any treatment group.

1.8.3 Pairwise meta-analyses

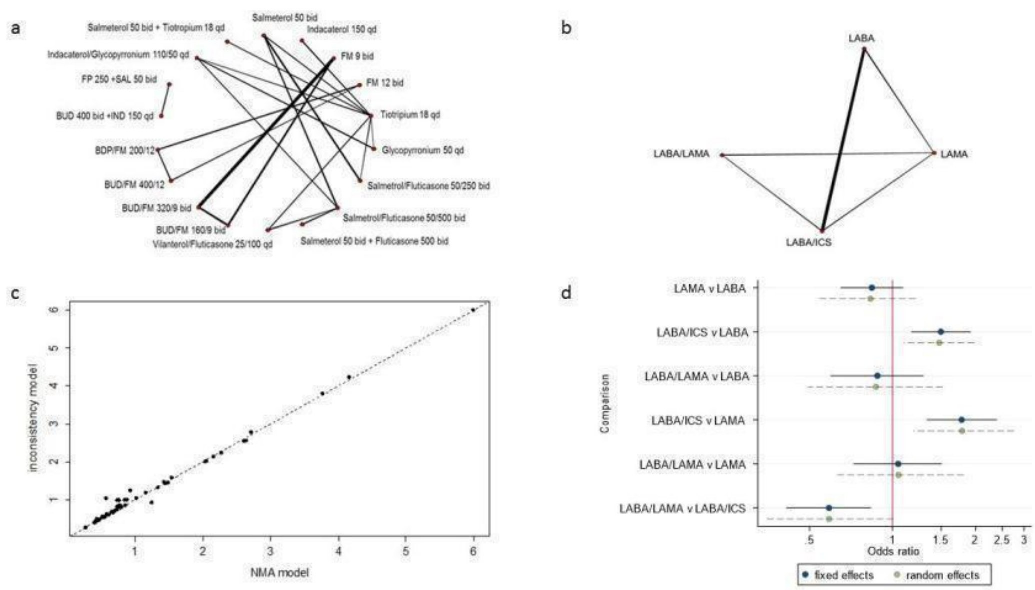
The results from pairwise MAs were consistent with the NMAs. There was no direct comparison for LABA/LAMA versus LABA (Appendix 6). The certainty of evidence was high for LAMA versus LABA, moderate for LABA/LAMA versus LABA/ICS, LABA/ICS versus LAMA, and low for LABA/LAMA versus LAMA and LABA/ICS versus LABA. There was no difference between random and fixed analyses.

1.9 Outcome: pneumonia

We included 24 studies of 18 interventions and four treatment groups for this outcome (Appendix 3; Figure 20 a and b). Note that interventions formoterol 9 μg twice daily, formoterol 12 μg twice daily, formoterol/budesonide 9 μg/160 μg twice daily, formoterol/budesonide 9 μg/320 μg twice daily, formoterol/budesonide 12 μg/400 μg twice daily, formoterol/beclomethasone 12 μg/200 μg twice daily, indacaterol 150 μg once daily + budesonide 400 μg twice daily, and salmeterol 50 μg twice daily + fluticasone 250 μg twice daily are disconnected from the main treatment network (Figure 20a), but we included them in a class/group model.

Figure 20. Pneumonia in the high-risk population

a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 1 favour the first named treatment group. BDP: beclomethasone; BUD: budesonide; FM: formoterol; FP: fluticasone propionate; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; SAL: salmeterol



1.9.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on a random-treatment-effects model with fixed-class effects for comparison. Results should be interpreted with some caution due to poor model fit, which can be attributed to studies with zero cells (Appendix 4).

1.9.2 NMA results

The NMA included a total of 31,812 participants (LABA: 10991, LAMA: 7853, LABA/ICS: 10413, LABA/LAMA: 2555). The median duration of follow-up was 52 weeks (range 12 to 156 weeks). Figure 20d and Table 33 show the OR of pneumonia for each treatment group compared to every other. There is evidence to suggest that LABA/ICS increases the odds of pneumonia compared to the other treatment groups (OR 1.69, 95% CrI 1.20 to 2.44; OR 1.78, 95% CrI 1.33 to 2.39; OR 1.50, 95% CrI 1.17 to 1.92 for LABA/LAMA, LAMA and LABA respectively), but no evidence of differences across other comparisons (Appendix 6 Summary of findings 7). Table 34 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group was LAMA with a median rank of 1st but with wide credible intervals (1st to 3rd), whereas LABA/ICS was ranked the worst (median = 4, 95% CrI 4th to 4th).

1.9.3 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs. There was no direct comparison for LABA/LAMA versus LABA (Appendix 6). The certainty of evidence was moderate for the all available comparisons (see 'Summary of findings' tables). There was no difference between random and fixed analyses.

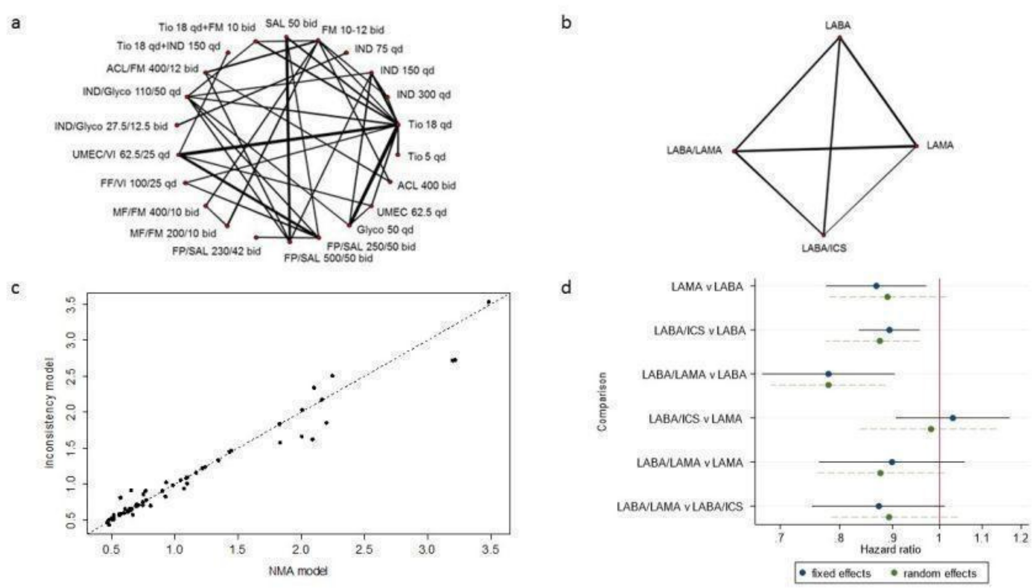
2. Results: low-risk population

2.1 Outcome: exacerbations

2.1.1 Outcome: moderate to severe exacerbations

We included 38 studies of 22 interventions and four treatment groups for this outcome (Appendix 3; Figure 21 a and b). Note that interventions indacaterol 75 μg once daily and indacaterol/glycopyrronium 27.5 μg/15.6 μg twice daily are disconnected from the main treatment network (Figure 21a), but we included them in a class/group model.

Figure 21. Moderate to severe exacerbations in the low-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 1 favour the first named treatment group. ACL: aclidinium; BUD: budesonide; FF: fluticasone furoate; FM: formoterol; FP: fluticasone propionate; Glyco: glycopyrronium; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; MF: mometasone furoate; SAL: salmeterol; Tio: tiotropium; UMEC: umeclidinium; VI: vilanterol



2.1.1.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on the random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

2.1.1.2 NMA results

The NMA included a total of 31,406 participants (LABA: 6845, LAMA: 7364, LABA/ICS: 9592, LABA/LAMA: 7605). The median duration of follow-up was 24 weeks (range 12 to 156 weeks). Figure 21d and Table 35 show the HR for moderate to severe exacerbations for each treatment group compared to every other. There is evidence that all treatment groups of interventions decrease the rate of moderate to severe exacerbations compared to LABA (HR 0.78, 95% CrI 0.67 to 0.90; HR 0.89, 95% CrI 0.84 to 0.96; HR 0.87, 95% CrI 0.78 to 0.97 for LABA/LAMA, LABA/ICS and LAMA respectively; Appendix 7; Summary of findings 7), although there is added uncertainty for the comparison with LAMA in the random-effects model. Table 36 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group is LABA/LAMA with a median rank of 1 (95% CrI 1st to 2nd) with LABA the worst ranked treatment group (95% CrI 4th to 4th).

2.1.1.3 Clinical homogeneity assessment

Table 37 shows the clinical homogeneity assessment across the available comparisons. Bronchial reversibility ranged from 11.1% to 17.5%, which could have introduced a bias favouring an ICS-containing inhaler in a population with a significant bronchodilator response. The NMA results should be interpreted with caution because of the difference in bronchial reversibility across the pairwise comparisons.

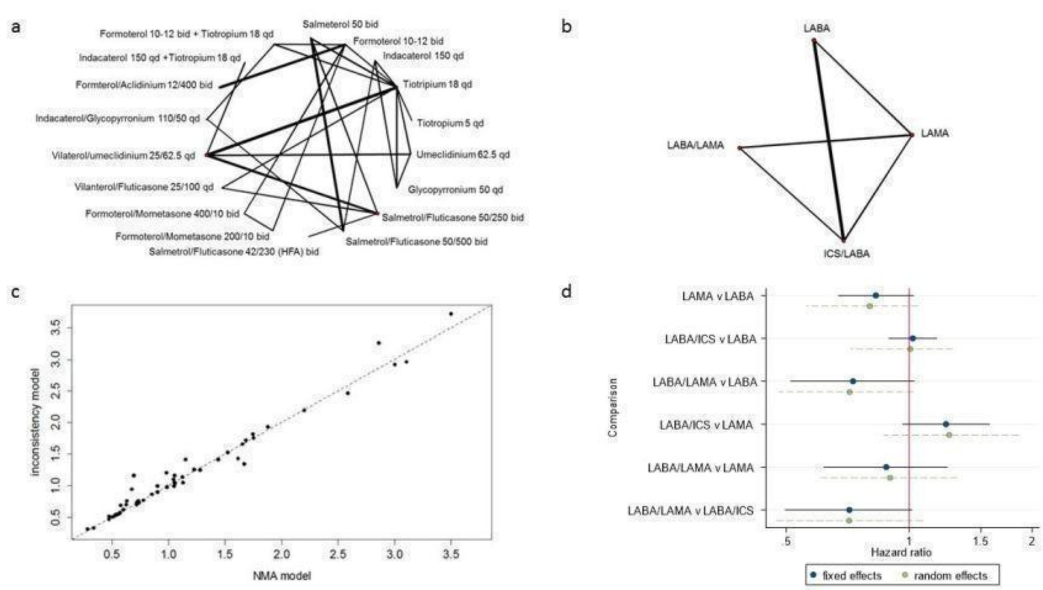
2.1.1.4 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs except for LAMA versus LABA, in which the 95% CI crossed the line of no difference with the pairwise MA (OR 0.92, 95% CI 0.79 to 1.07; Appendix 7). The certainty of evidence was moderate for the LAMA versus LABA comparison due to a suboptimal information size, which could explain the difference. Otherwise, the certainty of evidence was moderate for LABA/LAMA versus LABA/ICS and LABA/ICS versus LABA, and low for LABA/LAMA versus LAMA and LABA/ICS versus LAMA (see: 'Summary of findings' tables). There was no difference between random and fixed analyses.

2.1.2 Outcome: severe exacerbations

We included 31 studies of 18 interventions and four treatment groups for this outcome (Appendix 3; Figure 22 a and b).

Figure 22. Severe exacerbations in the low-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 1 favour the first named treatment group. ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.1.2.1 Model selection and inconsistency checking

We chose a fixed-effect model with fixed-class effects, assuming consistency. We also report results based on the random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

2.1.2.2 NMA results

The NMA included a total of 36,285 participants (LABA: 4963, LAMA: 17856, LABA/ICS: 7302, LABA/LAMA: 6164). The median duration of follow-up was 24 weeks (range 12 to 156 weeks). Figure 22d and Table 38 show the HR for severe exacerbations for each treatment group compared to every other. There is no evidence that any treatment group reduces severe exacerbations compared to the others, although uncertainty is large for some comparisons. HRs for LABA/LAMA versus LABA/ICS, LABA, and LAMA were 0.71 (95% CrI 0.47 to 1.08), 0.90, (95% CrI 0.6 to 1.31), and 0.72 (95% CrI 0.48 to 1.02), respectively (Appendix 7; Summary of findings 7). Table 39 shows the rank statistics for the four treatment groups (sorted by mean rank). There is considerable uncertainty in the ranks, which is consistent with there being no evidence of a difference in treatment effects between treatment groups. The highest ranked treatment group is LABA/LAMA with a median rank of 1 (95% CrI 1st to 3rd).

2.1.2.3 Clinical homogeneity assessment

Table 5 shows the clinical homogeneity assessment across the available comparisons. Bronchial reversibility ranged from 11.1% to 18.3%. The average bronchial reversibility for LABA/ICS versus LAMA was 11.1% which could have underestimated the effects of LABA/ICS. The NMA results should be interpreted with caution because of the difference in bronchial reversibility across the pairwise comparisons.

2.1.2.4 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs and showed no evidence that any treatment group reduced severe exacerbations compared to the others (Appendix 7). ORs for LABA/LAMA versus LABA/ICS, LAMA, and LABA were 0.66 (95% CI 0.27 to 1.63), 0.99 (95% CI 0.57 to 1.72), and 0.78 (95% CI 0.55 to 1.12). The certainty of evidence was high for LABA/ICS versus LABA, moderate for LABA/LAMA versus LABA/ICS, LABA/LAMA versus LAMA, and LABA/LAMA versus LABA, and low for LABA/ICS versus LAMA and LAMA versus LABA (see 'Summary of findings' tables). There was no difference between random and fixed analyses.

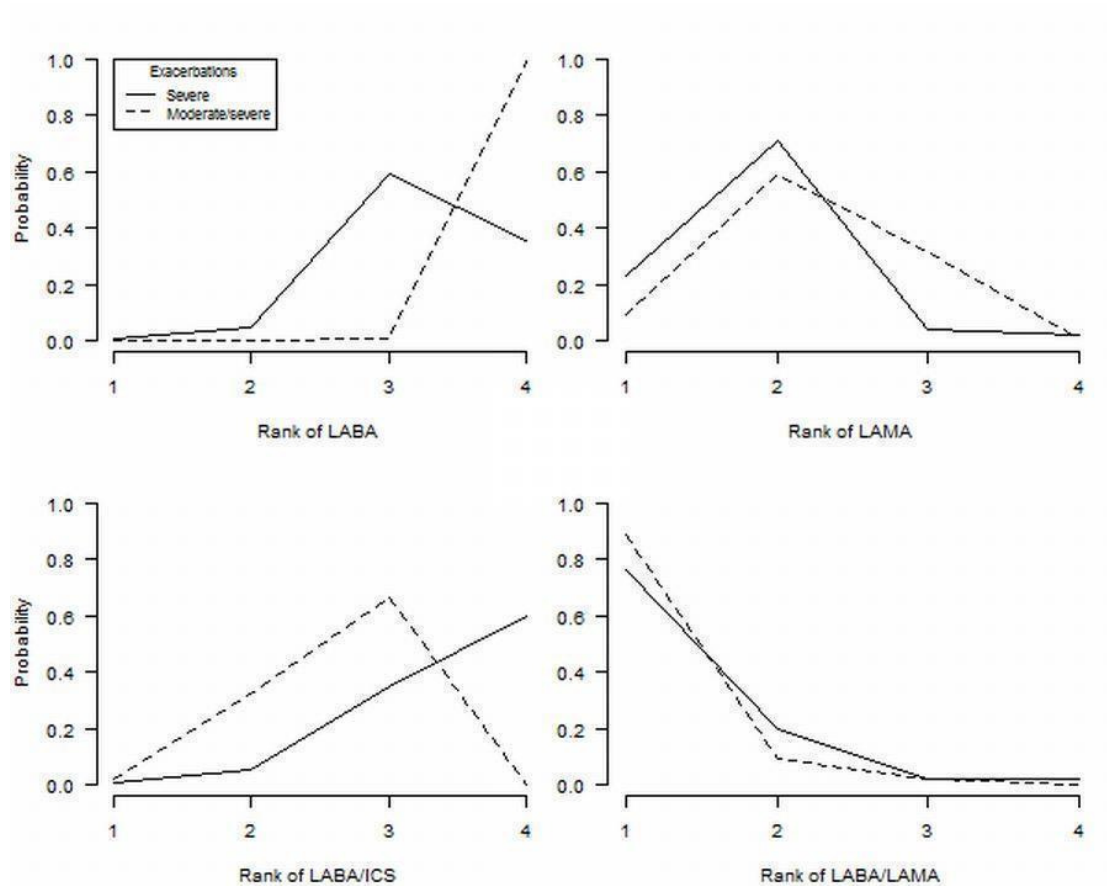
2.1.3 Rank probabilities for exacerbations

Figure 23 plots the ranks of each treatment group for severe exacerbations and moderate to severe exacerbations. The vertical axis shows the probability of being ranked best, second best, third best, or worst treatment group. LABA/LAMA has a high probability of being the best intervention for both severe and moderate to severe exacerbations in the low-risk population with a probability of about 90% of being the best treatment group to reduce moderate to severe exacerbations. LABA has a high probability of being the worst treatment group for reducing moderate to severe exacerbations and has a very small probability of ranking among the best treatment groups for reducing both severe and moderate to severe exacerbations.

Figure 23. Plot of rank probabilities for each treatment group for chronic obstructive pulmonary disease exacerbations in the low-risk population

Severe exacerbations (solid line), and moderate/severe exacerbations (dashed line), in the low-risk population

ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist

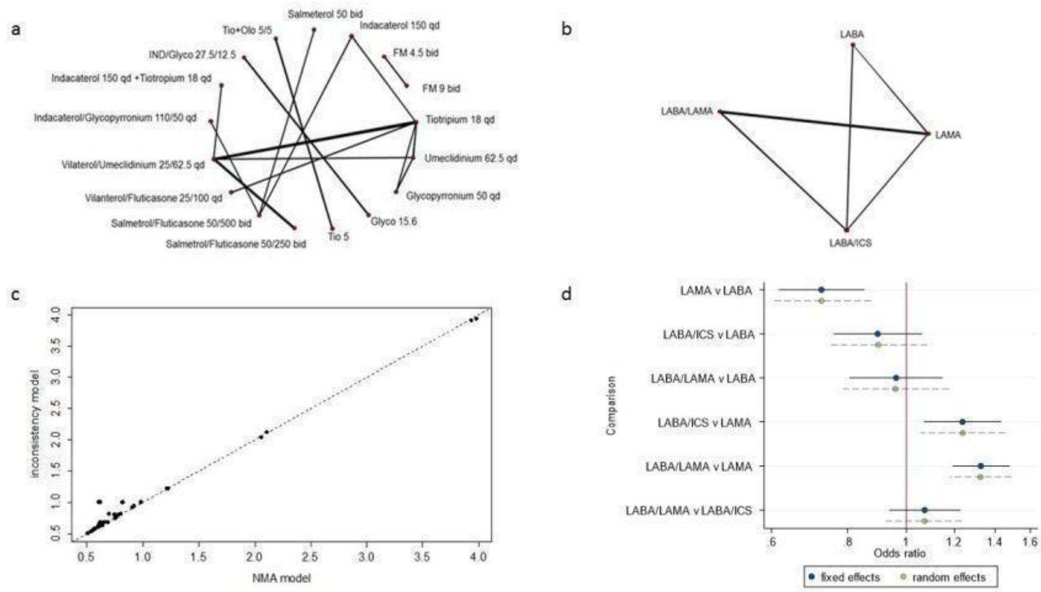


2.2 Outcome: St George's Respiratory Questionnaire (SGRQ) responders

2.2.1 Outcome: SGRQ responders at three months

We included 22 studies of 17 interventions and four treatment groups for this outcome (Appendix 3; Figure 24 a and b). Note that interventions formoterol 4.5 μg twice daily, formoterol 9 μg twice daily, glycopyrronium 15.6 μg twice daily, tiotropium 5 μg once daily, indacaterol/glycopyrronium 27.5 μg/15.6 μg twice daily and olodaterol/tiotropium 5 μg/5 μg once daily are disconnected from the main treatment network (Figure 24a), but we included them in a class/group model.

Figure 24. St George's Respiratory Questionnaire score responders at 3 months in the low-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values greater than 1 favour the first named treatment group. FM: formoterol; Glyco: glycopyrronium; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; Olo: olodaterol; Tio: tiotropium



2.2.1.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on the random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

2.2.1.2 NMA results

The NMA included a total of 14,351 participants (LABA: 2371, LAMA: 5356, LABA/ICS: 2213, LABA/LAMA: 4411). Figure 24d and Table 40 show the OR of SGRQ responders at three months for each treatment group compared to every other. There is evidence to suggest that LABA/LAMA, LABA/ICS, and LABA increase the odds of SGRQ response at three months compared to LAMA (OR 1.33, 95% CrI 1.19 to 1.48; OR 1.24, 95% CrI 1.07 to 1.43; OR 1.37, 95% CrI 1.18 to 1.61)). Table 41 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group was LABA with a median rank of 1 although with large uncertainty (95% CrI 1st to 3rd), whereas LAMA was ranked the worst (median = 4, 95% CrI 4th to 4th).

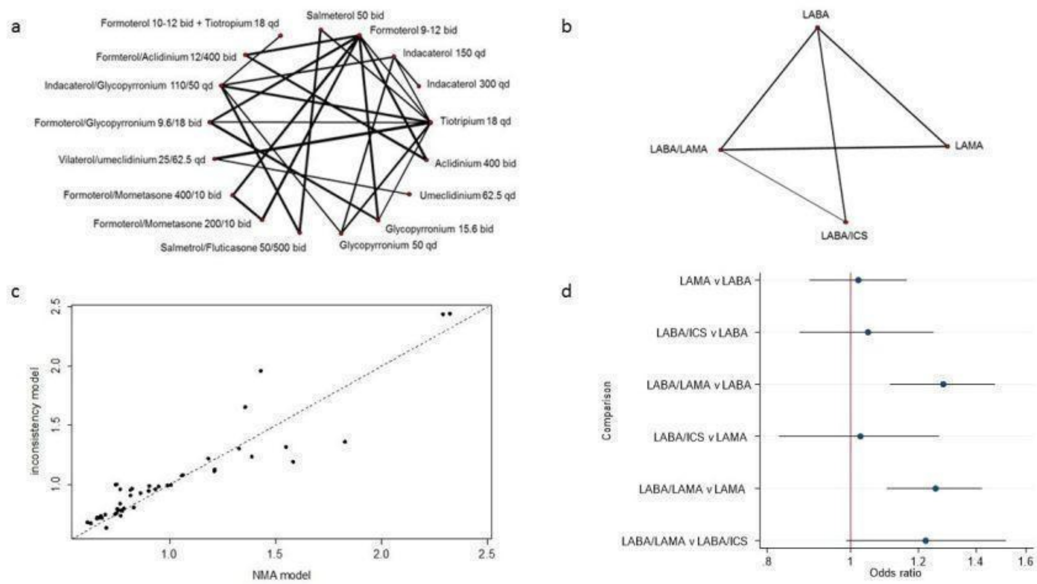
2.2.1.3 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs except for LABA/ICS versus LAMA (Appendix 7), in which the 95% CI crossed the line of no difference with the pairwise MA (OR 1.26 (95% CI 0.92 to 1.74), low confidence due to a wide 95% CI and a small sample size). There was no direct comparison for LABA/LAMA versus LABA. Otherwise, the certainty of evidence was high for LAMA/LABA versus LAMA, and LAMA versus LABA, and moderate for LABA/LAMA versus LABA/ICS, and low for LABA/ICS versus LABA. There was no difference between random and fixed analyses.

2.2.2 Outcome: SGRQ responders at six months

We included 18 studies of 19 interventions and four treatment groups for this outcome (Appendix 3; Figure 25 a and b).

Figure 25. St George's Respiratory Questionnaire score responders at 6 months in the low-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values greater than 1 favour the first named treatment group. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.2.2.1 Model selection and inconsistency checking

We chose a random-treatment-effects model with a fixed-class effect, assuming consistency (Appendix 4).

2.2.2.2 NMA results

The NMA included a total of 20,385 participants (LABA: 8259, LAMA: 5164, LABA/ICS: 2721, LABA/LAMA: 4241). Figure 25d and Table 42 show the OR of SGRQ responders at six months for each treatment group compared to every other. There is evidence to suggest that LABA/LAMA increases SGRQ responders at six months compared to both LAMA and LABA monotherapies (OR 1.26, 95% CrI 1.10 to 1.42; OR 1.28, 95% CrI 1.11 to 1.47). Table 43 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group is LABA/LAMA with a median rank of 1 (95% CrI 1st - 2nd), with LAMA and LABA the worst ranked treatment groups.

2.2.2.3 Pairwise meta-analyses

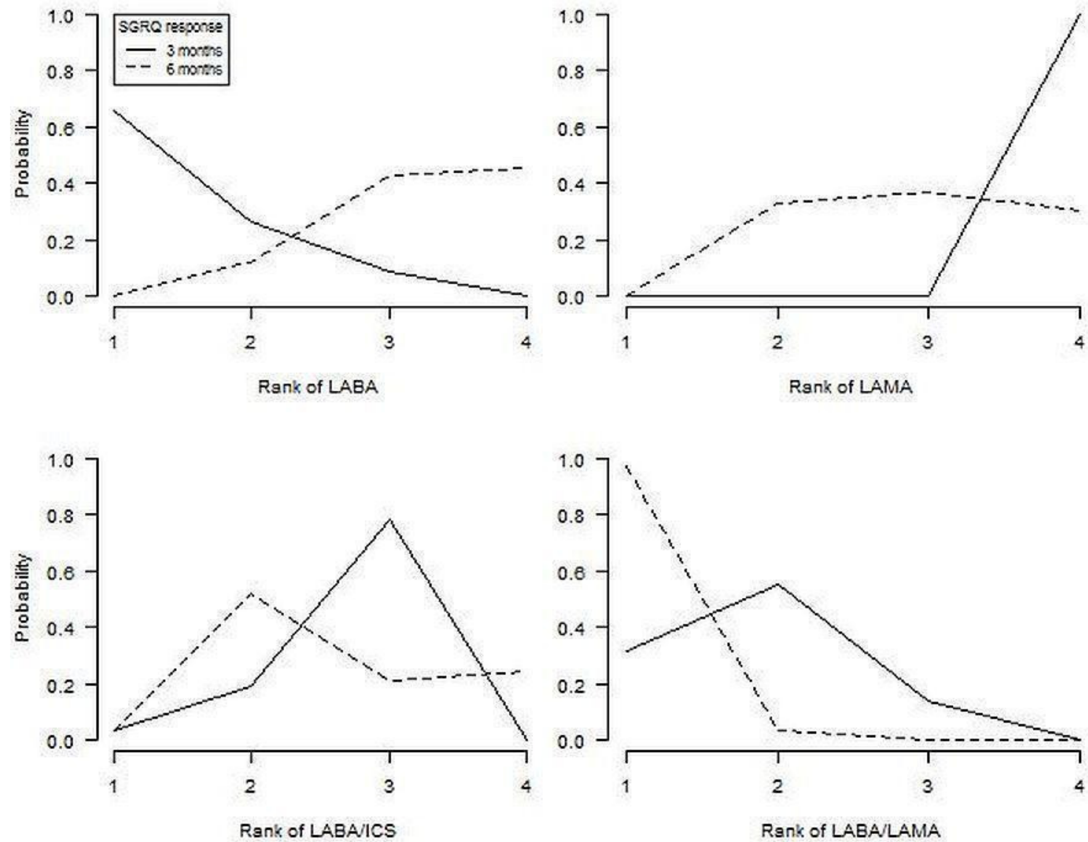
The results from pairwise MAs were consistent with the NMAs across all comparisons for SGRQ responders at six months (Appendix 7). There is evidence to suggest that LABA/LAMA increases SGRQ responders at six months compared to both LAMA and LABA monotherapies (OR 1.26, 95% CI 1.15 to 1.37; OR 1.20, 95% CI 1.06 to 1.37). The certainty of evidence was moderate for LABA/LAMA versus LAMA and LABA/ICS versus LABA and low for LABA/LAMA versus LABA/ICS, LABA/LAMA versus LABA, and LAMA versus LABA. There was no direct comparison for LABA/ICS versus LAMA. There was no difference between random and fixed analyses.

2.2.3 Rank probabilities for SGRQ responders at three and six months

Figure 26 plots the ranks of SGRQ responders at three and six months for each treatment group. The vertical axis shows the probability of being ranked best, second best, third best, or worst treatment group. There is uncertainty as to the ranking of treatment groups at three months but LAMA is clearly ranked worst. LABA has the highest probability of being ranked first at three months but there is also a small probability that it is ranked third or last. At six months, LABA/LAMA has nearly 100% probability of being the best.

Figure 26. Plot of rank probabilities for each treatment group for St George's Respiratory Questionnaire responders in the low-risk population

St George's Respiratory Questionnaire responders at 3 (solid line), and 6 months (dashed line), in the low-risk population ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.2.4 Outcome: SGRQ responders at 12 months

2.2.4.1 Pairwise meta-analyses

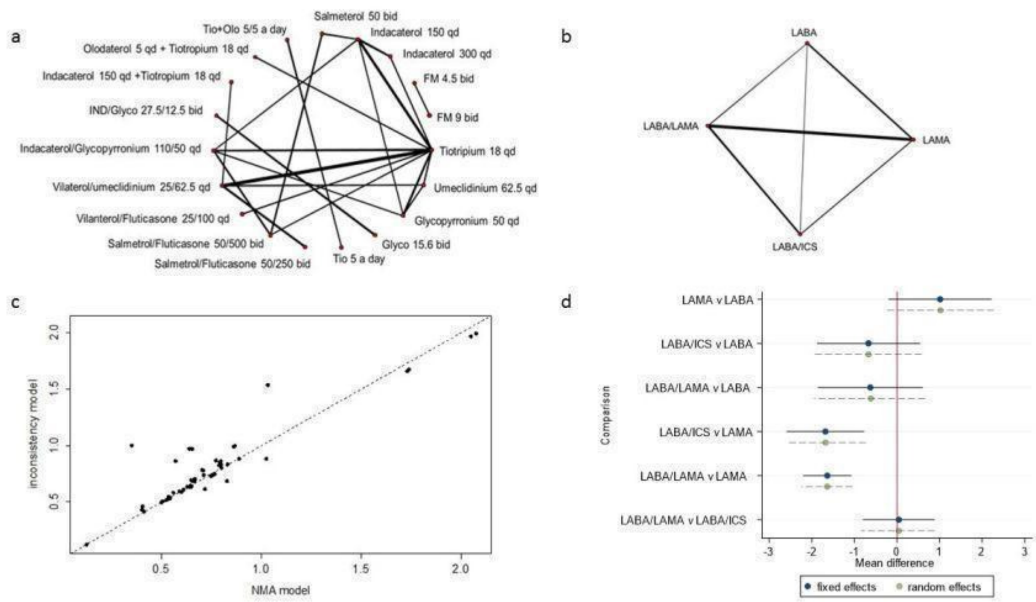
There is evidence to suggest LABA/ICS is associated with a significantly higher proportion in SGRQ responders at 12 months compared to LABA (OR 1.42, 95% CI 1.18 to 1.70; moderate-certainty evidence). There was no direct comparison for LABA/LAMA versus LABA/ICS and LABA/ICS versus LAMA. There is no evidence of significant differences for LABA/LAMA versus LAMA or LABA (moderate-certainty evidence), and LAMA versus LABA (low-certainty evidence; Appendix 7).

2.3 Outcome: change from baseline in SGRQ score

2.3.1 Outcome: change from baseline in SGRQ score at three months

We included 28 studies of 19 interventions and four treatment groups for this outcome (Appendix 3; Figure 27 a and b). Note that interventions formoterol 4.5 μg twice daily, formoterol 9 μg twice daily, glycopyrronium 15.6 μg twice daily, tiotropium 5 μg once daily, indacaterol/glycopyrronium 27.5 μg/15.6 μg twice daily, and olodaterol/tiotropium 5 μg/5 μg once daily are disconnected from the main treatment network (Figure 27a), but we included them in a class/group.

Figure 27. Change from baseline in SGRQ score at 3 months in the low-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 0 favour the first named treatment group. FM: formoterol; Glyco: glycopyrronium; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; Olo: olodaterol; Tio: tiotropium



2.3.1.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on the random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

2.3.1.2 NMA results

The NMA included a total of 20,594 participants (LABA: 3933, LAMA: 7849, LABA/ICS: 2396, LABA/LAMA: 6416). Figure 27d and Table 44 show the mean difference in change from baseline in SGRQ score at three months for each treatment group compared to every other. There is evidence to suggest that both LABA/LAMA and LABA/ICS improve SGRQ score at three months compared to LAMA (MD −1.64, 95% CrI −2.2 to −1.08; MD −1.68, 95% CrI −2.59 to −0.78), although the MDs do not reach the clinical significance of MCID of 4. There is no evidence of differences across the other comparisons. Table 45 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment groups are LABA/ICS and LABA/LAMA, both with a median rank of 2 (95% CrI 1st to 3rd).

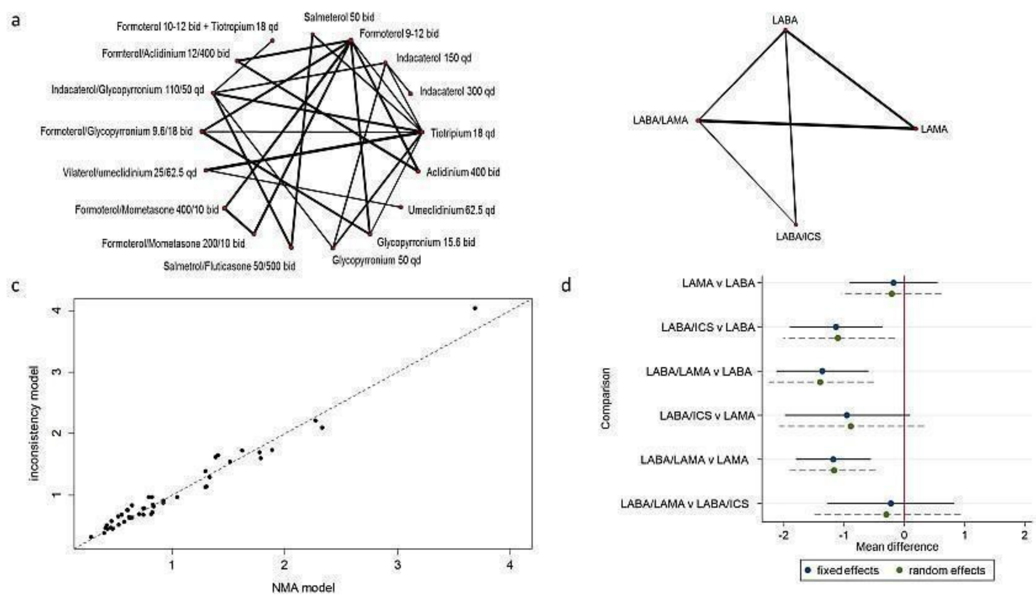
2.3.1.3 Pairwise meta-analyses

There is evidence to suggest that LABA/LAMA improves SGRQ score at three months compared to LAMA (MD −1.60, 95% CI −2.19 to −1.01), and that LAMA improves the score compared to LABA (MD 1.84, 95% CI 0.87 to 2.80), but the mean differences do not reach the clinical significance of MCID of 4. There is no evidence of differences across the other comparisons, however, a clinically significant difference cannot be excluded favouring LABA/LAMA over LABA given its 95% CI crossing the line of MCID of 4 (MD −1.29, 95% CI −4.29, 1.71; Appendix 7). The certainty of evidence for LABA/ICS versus LAMA and LAMA versus LABA was moderate due to a suboptimal information size, which could explain discrepancies with the NMA results. Otherwise all other results were consistent with the NMAs. The certainty of evidence was moderate for LABA/LAMA versus LAMA or LABA and high for LABA/LAMA versus LABA/ICS and LABA/ICS versus LABA. There was no difference between random and fixed analyses.

2.3.2 Outcome: change from baseline in SGRQ score at six months

We included 20 studies of 17 interventions and four treatment groups for this outcome (Appendix 3; Figure 28 a and b).

Figure 28. Change from baseline in St George's Respiratory Questionnaire score at 6 months in the low-risk population. a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 0 favour the first named treatment group. FM: formoterol; Glyco: glycopyrronium; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; Olo: olodaterol; Tio: tiotropium



2.3.2.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on the random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

2.3.2.2 NMA results

The NMA included a total of 16,508 participants (LABA: 4351, LAMA: 4454, LABA/ICS: 2880, LABA/LAMA: 4823). Figure 28d and Table 46 show the mean difference in change from baseline in SGRQ score at six months for each treatment group compared to every other. There is evidence to suggest that both LABA/LAMA and LABA/ICS reduce SGRQ score compared to LABA at six months (MD −1.36, 95% CrI −2.12 to −0.60; MD −1.14, 95% CrI −1.90 to −0.37), and that LABA/LAMA reduces SGRQ score compared to LAMA (MD −1.18, 95% CrI −1.80 to -0.56), although the differences do not reach the clinical significance of MCID of 4. Table 47 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group was LABA/LAMA with a median rank of 1 (95% CrI 1st to 2nd).

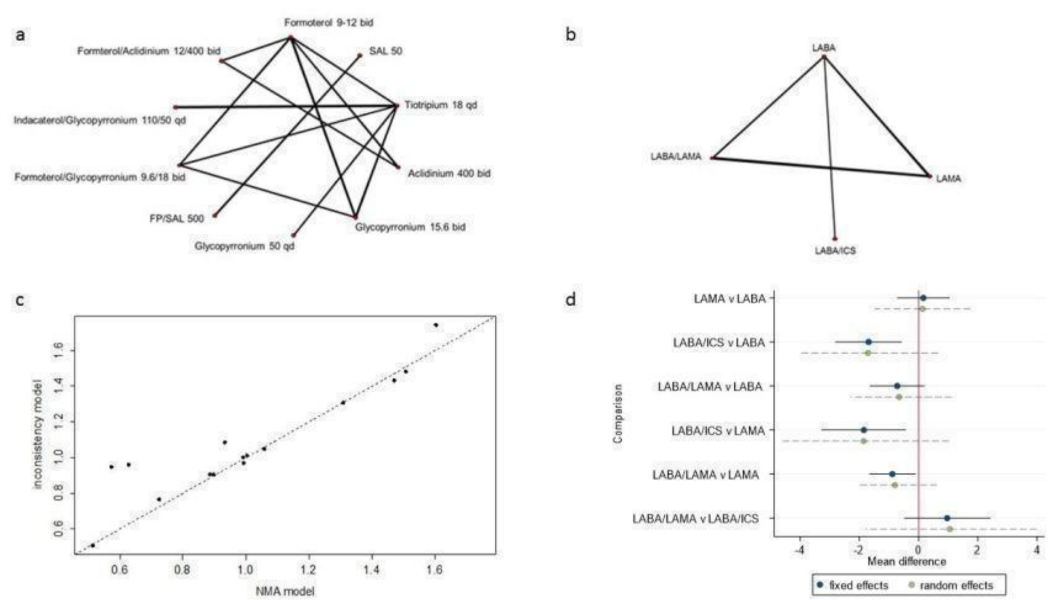
2.3.2.3 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs and there is no evidence of clinically significant improvement in SGRQ score at six months (MCID of 4 or greater), with any treatment group compared to the others (Appendix 7). There were no data available for LABA/ICS versus LAMA. The certainty of evidence was high for LAMA versus LABA, moderate for LABA/LAMA versus LAMA or LABA and LABA/ICS versus LABA, and low for LABA/LAMA versus LABA/ICS. There was no difference between random and fixed analyses.

2.3.3 Outcome: change from baseline in SGRQ score at 12 months

We included six studies of 10 interventions and four treatment groups for this outcome (Appendix 3; Figure 29 a and b). Note that interventions salmeterol 50 μg twice daily and salmeterol/fluticasone 50 μg/500 μg twice daily are disconnected from the main treatment network (Figure 29a), but we included them in a class/group model.

Figure 29. Change from baseline in SGRQ score at 12 months in the low-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 0 favour the first named treatment group. FP: fluticasone propionate; ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; SAL: salmeterol



2.3.3.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on the random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

2.3.3.2 NMA results

The NMA included a total of 6849 participants (LABA: 2021, LAMA: 2163, LABA/ICS: 873, LABA/LAMA: 1792). Figure 29d and Table 48 show the mean difference in change from baseline in SGRQ score at 12 months for each treatment group compared to every other. There is some evidence to suggest that LABA/ICS improves SGRQ score at 12 months compared to LABA using the fixed-effect model (MD −1.69, 95% CrI −2.81 to −0.57). Both LABA/LAMA and LABA/ICS showed a reduction in SGRQ score compared to LAMA when using the fixed effect model (MD −0.89, 95% CrI −1.66 to −0.11) and MD −1.85, 95% CrI −3.28 to −0.43). Increased uncertainty in the random-effects model leads to inconclusive results and the mean differences do not reach the clinical significance of MCID of 4. Table 49 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group is LABA/ICS with a median rank of 1 (95% CrI 1st to 2nd).

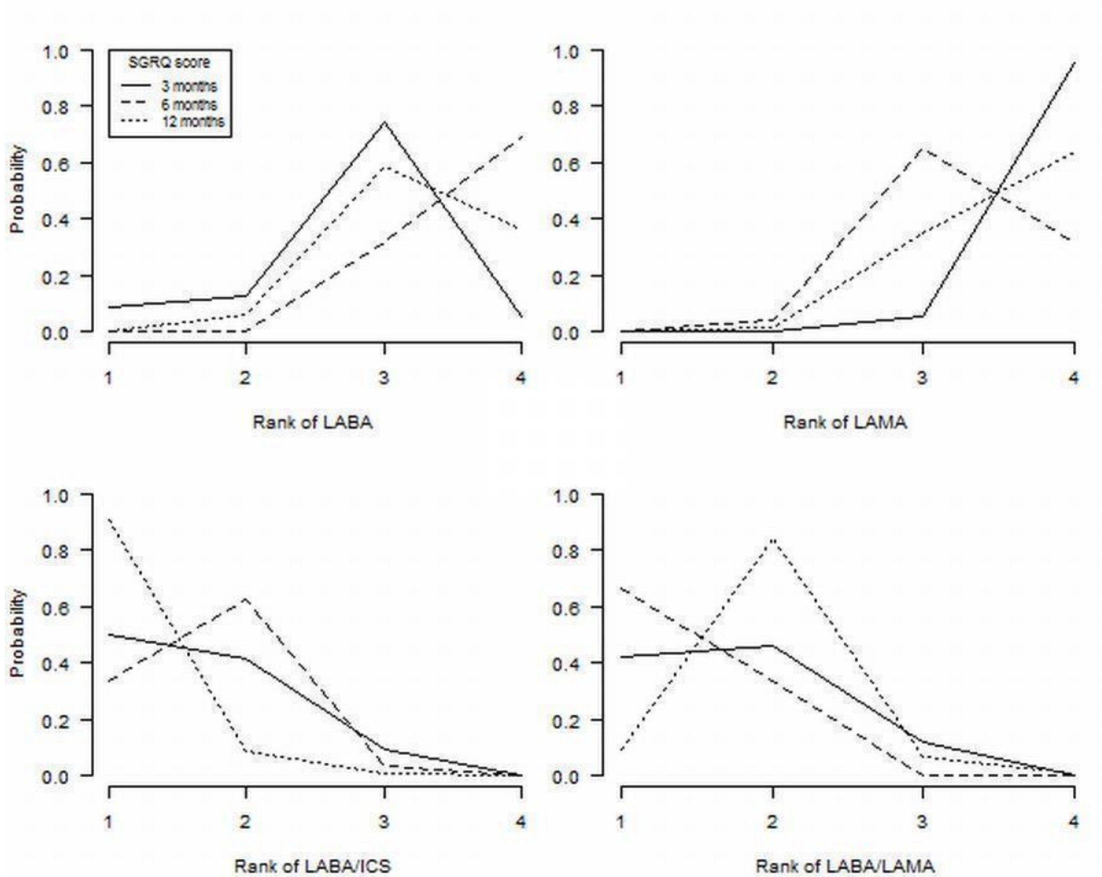
2.3.3.3 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs and there is no evidence that any treatment group is associated with clinically significant improvement in SGRQ score at 12 months compared to the others (Appendix 7). The certainty of evidence was high for LABA/LAMA versus LABA and LAMA versus LABA, moderate for LABA/ICS versus LABA, and very low for LABA/LAMA versus LAMA. There was no direct comparison for LABA/LAMA versus LABA/ICS and LABA/ICS versus LAMA. There was no difference between random and fixed analyses.

2.3.4 Rank probabilities for change from baseline in SGRQ score

Figure 30 plots the ranks of SGRQ score at 3, 6 and 12 months for each treatment group. The vertical axis shows the probability of being ranked best, second best, third best, or worst treatment group. LABA and LAMA have a high probability of ranking 3rd or 4th at all time points whereas LABA/ICS has a high probability of being the best at 12 months.

Figure 30. Plot of rank probabilities for each treatment group
Change from baseline in St George's Respiratory Questionnaire score at 3 (solid line), 6 (dashed line), and 12 months (dotted line), in the low-risk population ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist

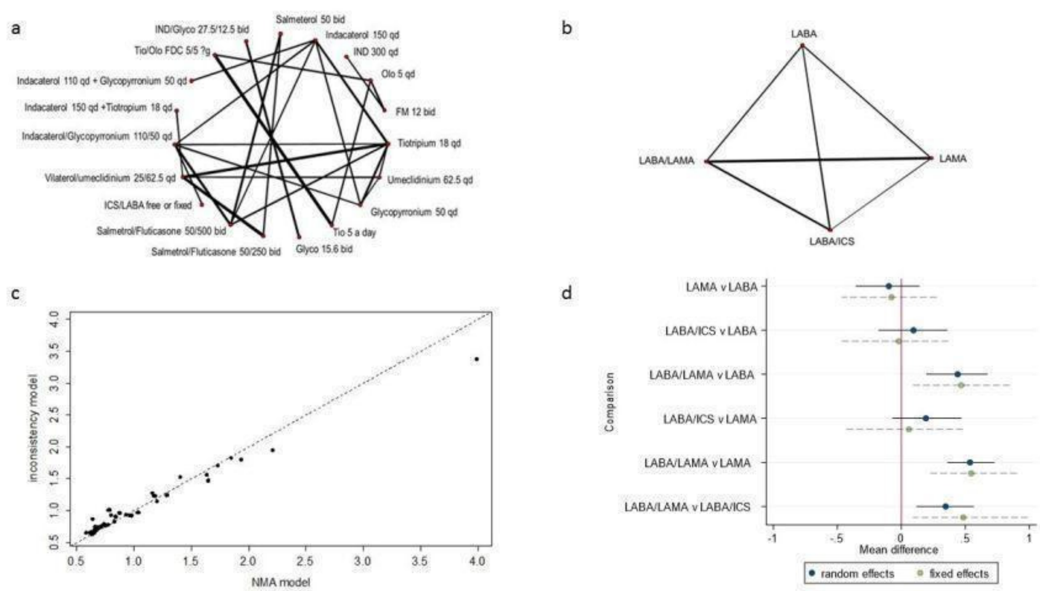


2.4 Outcome: transitional dyspnoea index (TDI)

2.4.1 Outcome: TDI at three months

We included 30 studies of 19 interventions and four treatment groups for this outcome (Appendix 3; Figure 31 a and b). Note that interventions glycopyrronium 15.6 μg twice daily and indacaterol/glycopyrronium 27.5 μg/15.6 μg twice daily are disconnected from the main treatment network (Figure 31a), but we included them in a class/group model.

Figure 31. Transition Dyspnea Index at 3 months in the low-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Positive values favour the first named treatment group. FM: formoterol; Glyco: glycopyrronium; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; Olo: olodaterol; Tio: tiotropium



2.4.1.1 Model selection and inconsistency checking

We chose a random-treatment-effects model with fixed-class effects, assuming consistency. We also report results for a fixed-treatment-effect model with random-class effects for comparison (Appendix 4).

2.4.1.2 NMA results

The NMA included a total of 21,750 participants (LABA: 5113, LAMA: 7046, LABA/ICS: 2838, LABA/LAMA: 6753). Figure 31d and Table 50 show the mean difference in TDI score at three months for each treatment group compared to every other, using the two models. There is evidence to suggest that LABA/LAMA increases TDI at three months compared to all other treatment groups (MD 0.35, 95% CrI 0.12 to 0.56; MD 0.54, 95% CrI

0.36 to 0.73; MD 0.44, 95% CrI 0.20 to 0.67 against LABA/ICS, LAMA and LABA), although the MDs do not reach the clinical significance of MCID of 1. There is no evidence of differences across the other treatment groups using the model with random-treatment and fixed-class effects. Table 51 shows the rank statistics for the four treatment groups (sorted by mean rank) for the preferred model. The highest ranked treatment group was LABA/LAMA with a median rank of 1 (95% CrI 1st to 1st).

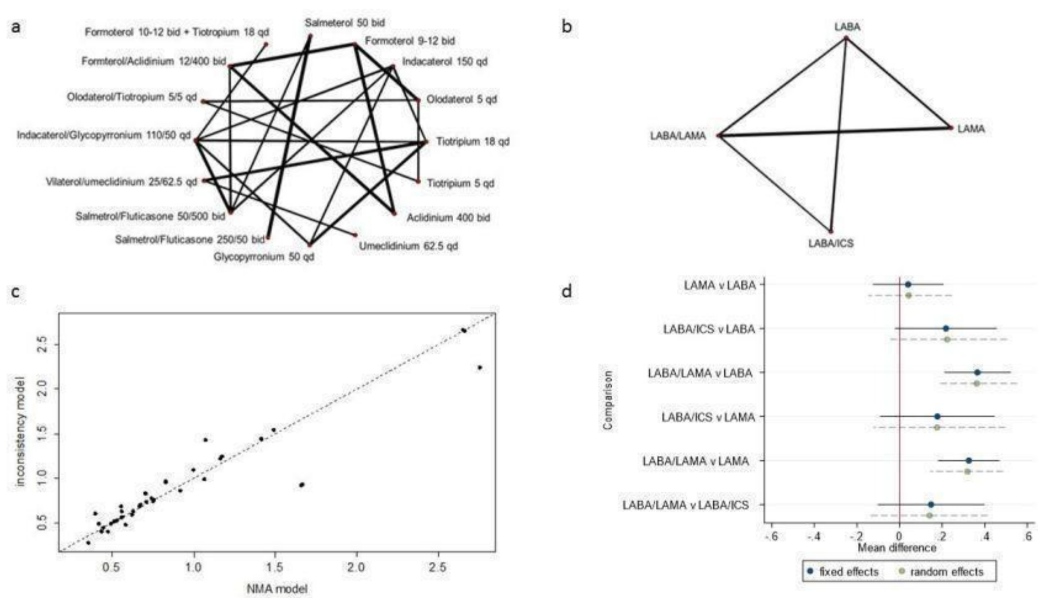
2.4.1.3 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs and there is no evidence that any treatment group is associated with clinically significant improvement in TDI at three months (MCID of 1), compared to the others, despite a significant difference in some comparisons (Appendix 7). The certainty of evidence was high for LABA/ICS versus LABA, moderate for LABA/LAMA versus LAMA, low for LABA/LAMA versus LABA/ICS or LABA, and very low for LABA/ICS versus LAMA. There was no difference between random and fixed analyses.

2.4.2 Outcome: TDI at six months

We included 18 studies of 16 interventions and four treatment groups for this outcome (Appendix 3; Figure 32 a and b).

Figure 32. Transition Dyspnea Index at 6 months in the low-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Positive values favour the first named treatment group. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.4.2.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on a random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

2.4.2.2 NMA results

The NMA included a total of 14,315 participants (LABA: 3878, LAMA: 3977, LABA/ICS: 1825, LABA/LAMA: 4635). Figure 32d and Table 52 show the mean difference in TDI score at six months for each treatment group compared to every other. There is evidence to suggest that LABA/LAMA increases TDI at six months compared to LAMA and LABA monotherapies (MD 0.33, 95%

CrI 0.18 to 0.47; MD 0.37, 95% CrI 0.21, 0.52), although the MDs do not reach the clinical significance of MCID of 1. There is no evidence of differences across the other comparisons. Table 53 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group is LABA/LAMA with a median rank of 1 (95% CrI 1st to 2nd).

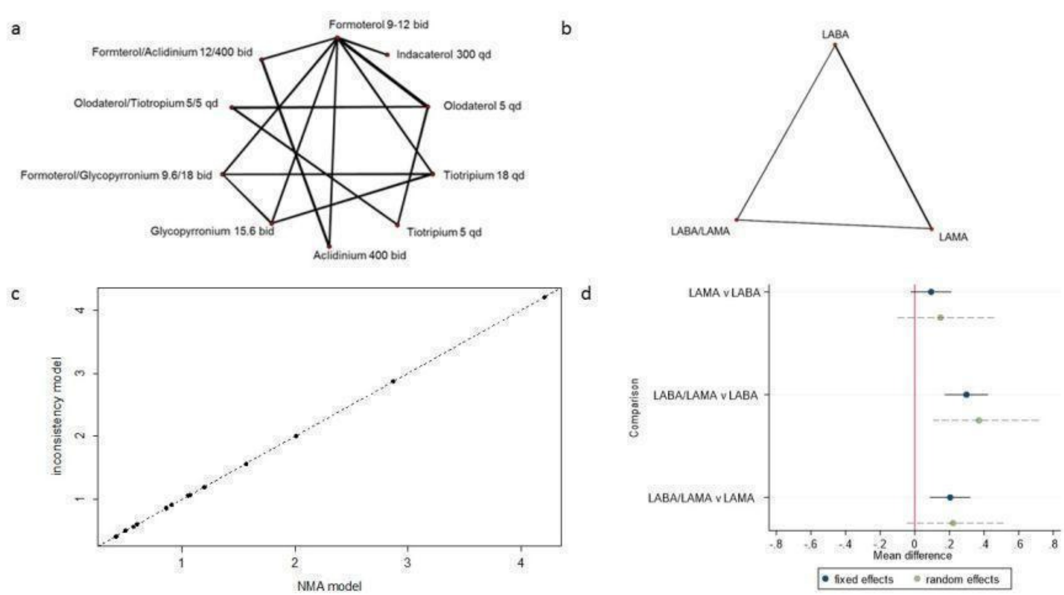
2.4.2.3 Pairwise meta-analyses

There was no direct comparison for LABA/ICS versus LAMA. Otherwise, the results from pairwise MAs were consistent with the NMAs and there is no evidence that any treatment group is associated with clinically significant improvement in TDI at six months (MCID of 1), compared to the others (Appendix 7). The certainty of evidence was high for LABA/LAMA versus LABA/ICS and LABA/ICS versus LABA, moderate for LABA/LAMA versus LAMA or LABA, and low for LAMA versus LABA. There was no difference between random and fixed analyses .

2.4.3 Outcome: TDI at 12 months

We included six studies of 10 interventions and three treatment groups for this outcome (Appendix 3; Figure 33 a and b).

Figure 33. Transition Dyspnea Index at 12 months in the low-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Positive values favour the first named treatment group. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.4.3.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on the random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

2.4.3.2 NMA results

The NMA included a total of 38,861 participants (LABA: 3908, LAMA: 32,624, LABA/ICS: 0, LABA/LAMA: 2329). Figure 33d and Table 54 show the mean difference in TDI score at 12 months for each treatment group compared to every other. There is evidence to suggest that LABA/LAMA increases TDI at 12 months compared to LAMA and LABA monotherapies (MD 0.20, 95% CrI 0.09 to 0.32; MD 0.30, 95% CrI 0.17 to 0.42). There is no evidence of differences across other comparisons. Table 55 shows the rank statistics for the three treatment groups (sorted by mean rank). The highest ranked treatment group was LABA/LAMA with a median rank of 1 (95% CrI 1st to 1st).

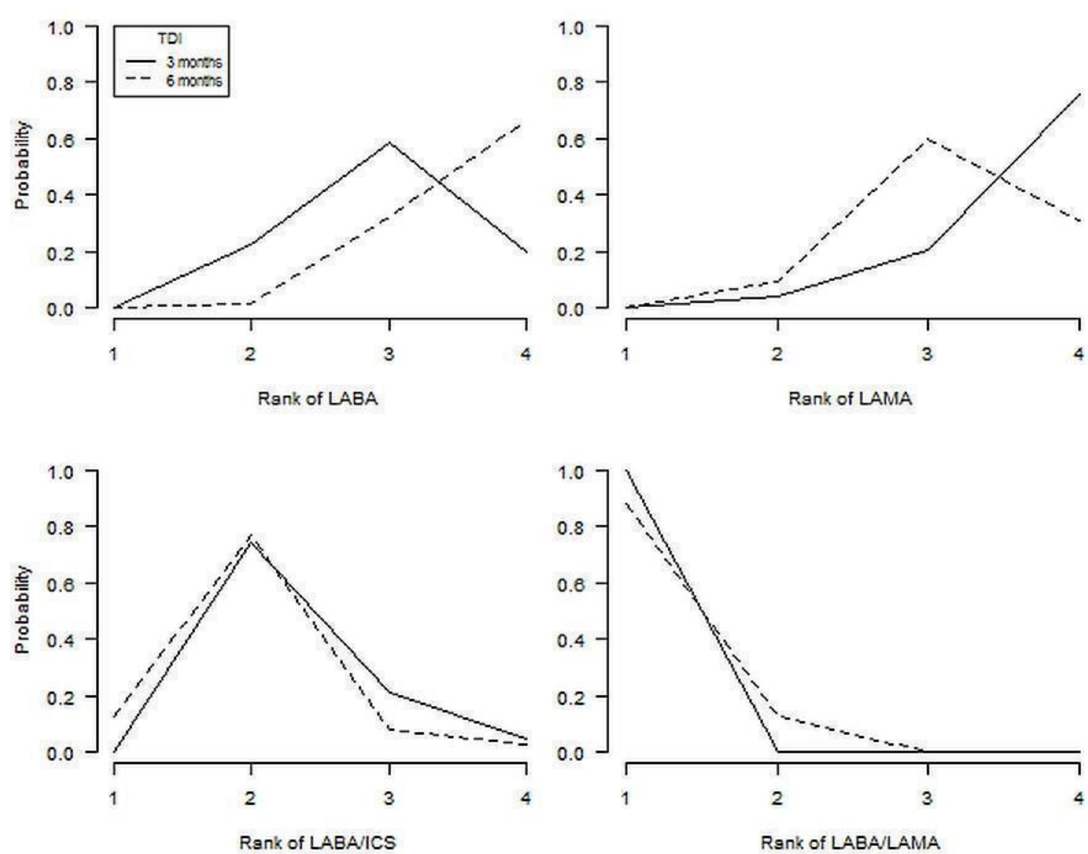
2.4.3.3 Pairwise meta-analyses

There was no direct comparison for LABA/LAMA versus LABA/ICS and LABA/ICS versus LAMA or LABA. Otherwise, the results from pairwise MAs were consistent with the NMAs and there is no evidence that any treatment group is associated with clinically significant improvement in TDI at 12 months (MCID of 1), compared to the others (Appendix 7). The certainty of evidence was high for LAMA versus LAMA, moderate for LABA/LAMA versus LAMA, and very low for LABA/LAMA versus LABA. There was no difference between random and fixed analyses.

2.4.4 Rank probabilities for TDI

Figure 34 plots the ranks of TDI score for each treatment group at three and six months only. Ranks at 12 months are not plotted as only three treatment groups were available for comparison. The vertical axis shows the probability of being ranked best, second best, third best, or worst treatment group. LABA/LAMA has the highest probability of being ranked first at six months and nearly 100% probability of being the best at three months. There is uncertainty in the ranking of the other interventions.

Figure 34. Plot of rank probabilities for each treatment group for Transition Dyspnea Index
Transition Dyspnea Index score at 3 and 6 months in the low-risk population. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist

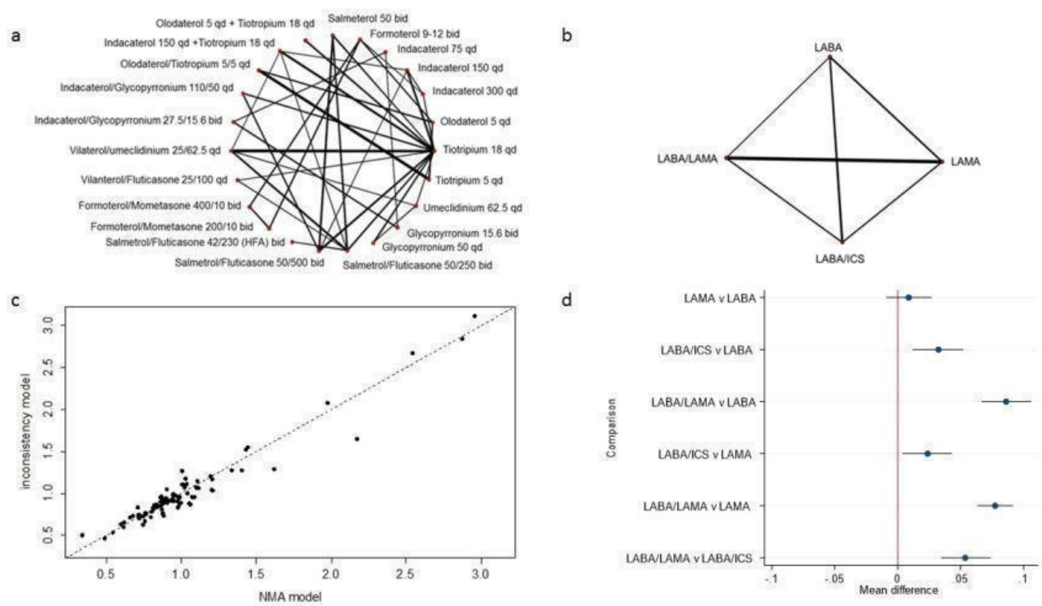


2.5 Outcome: change from baseline in forced expiratory volume in one second (FEV1)

2.5.1 Outcome: change from baseline in FEV1 at three months

We included 50 studies of 23 interventions and four treatment groups for this outcome (Appendix 3; Figure 35 a and b). Note that interventions indacaterol 75 μg once daily, glycopyrronium 15.6 μg twice daily and indacaterol/glycopyrronium 27.5/12.5 μg twice daily are disconnected from the main treatment network (Figure 35a), but we included them in a class/group model.

Figure 35. Change from baseline in forced expiratory volume in 1 second at 3 months in the low-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Positive values favour the first named treatment group. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.5.1.1 Model selection and inconsistency checking

We chose a random-treatment-effects model with fixed-class effects, assuming consistency (Appendix 4).

2.5.1.2 NMA results

The NMA included a total of 30,962 participants (LABA: 6725, LAMA: 9977, LABA/ICS: 6126, LABA/LAMA: 8134) Figure 35d and Table 56 show the mean difference in change from baseline in FEV1 at three months for each treatment group compared to every other. There is evidence to suggest that LABA/LAMA and LABA/ICS increase FEV1 at three months compared to LAMA (MD 0.08, 95% CrI 0.06 to 0.09; MD 0.02, 95% CrI 0 to 0.04), and LABA (MD 0.09, 95% CrI 0.07 to 0.11; 0.03 95% CrI 0.01 to 0.05), monotherapies and that LABA/LAMA improves FEV1 compared to LABA/ICS (MD 0.05, 95% CrI 0.03 to 0.07). The 95% CI exceeding MCID of 0.1 L suggests a possibility of clinically significant improvement favouring LABA/LAMA over LABA. Table 57 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group was LABA/LAMA with a median rank of 1 (95% CrI 1st to 1st).

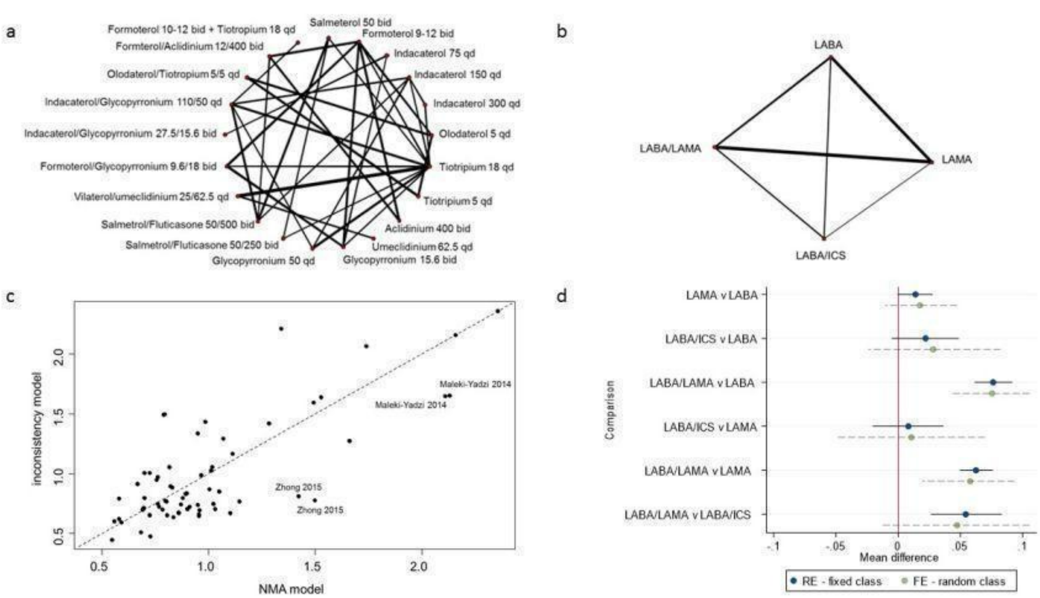
2.5.1.3 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs and there is no evidence that any treatment group is associated with clinically significant improvement (MCID of 0.1 L) in change from baseline in FEV1 at three months compared to the others (Appendix 7). However, a clinically significant improvement in change from baseline in FEV1 at three months cannot be excluded favouring LABA/LAMA over LABA/ICS (MD 0.08, 95% CI 0.03 to 0.12; low-certainty evidence), and LABA (MD 0.07, 95% CI 0.03 to 0.12; very low-certainty evidence), given the 95% CI crossing the line of MCID of 0.1 L. Otherwise, the certainty of evidence was moderate for LABA/ICS versus LABA, low for LABA/LAMA versus LABA/ICS or LAMA, LABA/ICS versus LAMA, and LAMA versus LABA. There was no difference between random and fixed analyses except for LABA/ICS versus LAMA, in which the random-effects model had a wider 95% CI containing the line of no difference (MD 0.02, 95% CI −0.02 to 0.06).

2.5.2 Outcome: change from baseline in FEV1 at six months

We included 30 studies of 21 interventions and four treatment groups for this outcome (Appendix 3; Figure 36 a and b).

Figure 36. Change from baseline in forced expiratory volume in 1 second at 6 months in the low-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot (deviance points from the fixed-effect model with random-treatment-group effect on the x-axis and from the fixed-effect inconsistency model with random-class effect on the y-axis); d. plot of relative effects. Positive values favour the first named treatment group. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.5.2.1 Model selection and inconsistency checking

We chose a random-treatment-effects model with fixed-class effects, assuming consistency. We also report results for a fixed-treatment-effect model with random-class effects for comparison. However, there is weak evidence of potential inconsistency in this network and results should be interpreted with some caution (Appendix 4).

2.5.2.2 NMA results

The NMA included a total of 21,224 participants (LABA: 5959, LAMA: 6360, LABA/ICS: 2155, LABA/LAMA: 6750). Figure 36d and Table 58 show the mean difference in change from baseline in FEV1 at six months for each treatment group compared to every other. There is evidence to suggest that LABA/LAMA increases FEV1 at six months compared to all other treatment groups (MD 0.05, 95% CrI 0.03 to 0.08; MD 0.06, 95% CrI 0.05 to 0.08; MD 0.08, 95% CrI 0.06 to 0.09 against LABA/ICS, LAMA, and LABA respectively), and that LAMA slightly increases FEV1 compared to LABA (MD 0.01, 95% CrI 0.00 to 0.03), in the random-effects-model with fixed-class effects although the mean differences do not reach the clinical significance of MCID of 0.1 L. Table 59 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group was LABA/LAMA with a median rank of 1 (95% CrI 1st to 1st). Results are more uncertain when considering the fixed-treatment-effect model with random-class effects.

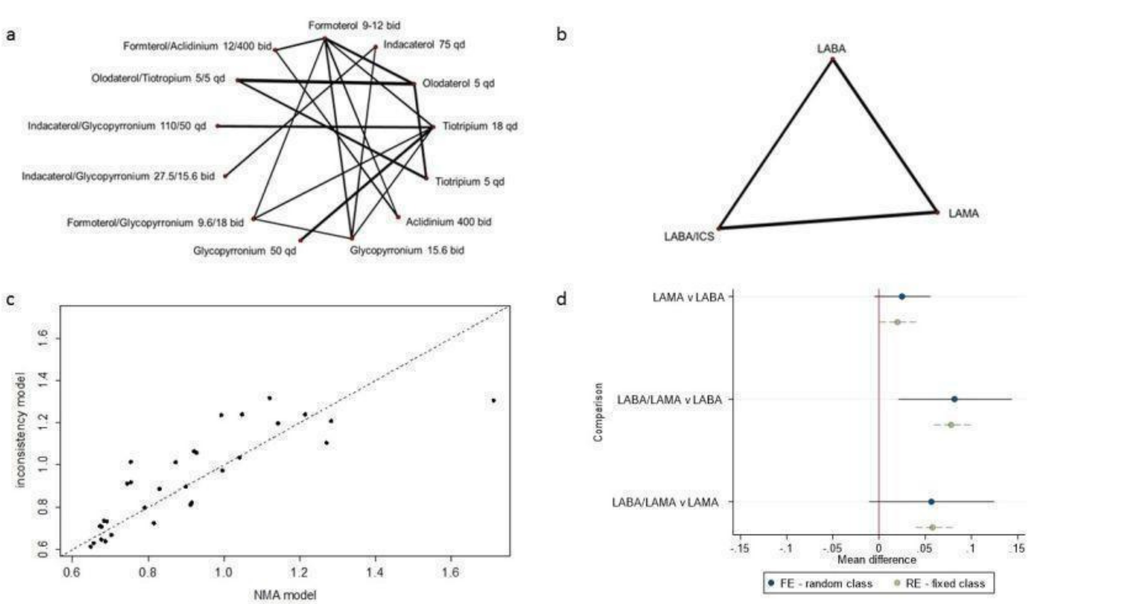
2.5.2.3 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs except for LABA/ICS versus LABA in which LABA/ICS significantly increased FEV1 at six months compared to LABA (MD 0.04, 95% CI 0.01 to 0.07). There is no evidence of clinically significant improvement (MCID of 0.1 L or greater) with any treatment group compared to the others, except for LABA/LAMA versus LABA/ICS in which its 95% CI suggested a possibility of clinically significant difference favouring LABA/LAMA over LABA/ICS (MD 0.10, 95% CI 0.05 to 0.15; Appendix 7). The certainty of evidence was high for LABA/LAMA versus LABA/ICS and LABA/ICS versus LAMA, and moderate for LABA/LAMA versus LAMA and LABA/ICS versus LABA. There was no difference between random and fixed analyses.

2.5.3 Outcome: change from baseline in FEV1 at 12 months

We included 13 studies of 13 interventions and three treatment groups for this outcome (Appendix 3; Figure 37 a and b).

Figure 37. Change from baseline in forced expiratory volume in 1 second at 12 months in the low-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot (deviance points from the fixed-effect model with random-class effect on the x-axis and from the fixed-effect inconsistency model with random-class effect on the y-axis); d. plot of relative effects. Positive values favour the first named treatment group. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.5.3.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with random-class effects, assuming consistency. We also reported results for a random-treatment-effects model with fixed-class effects for comparison. However, there is weak evidence of potential inconsistency in the latter model so results should be interpreted with caution (Appendix 4).

2.5.3.2 NMA results

The NMA included a total of 10,676 participants (LABA: 3577, LAMA: 4057, LABA/ICS: 0, LABA/LAMA: 3042). Figure 37d and Table 60 show the mean difference in change from baseline in FEV1 at 12 months for each treatment group compared to every other. There is evidence to suggest that LABA/LAMA increases FEV1 at 12 months compared to LABA (MD 0.08, 95% CrI 0.02 to 0.14). However there is high uncertainty in the results. Comparisons based on the random-treatment-effects model with fixed class are more precise with similar MDs. The 95% CI containing MCID of 0.1 L in both models (MD 0.08, 95% CrI 0.02 to 0.14 and MD 0.08, 95% CrI 0.06 to 0.1), suggests a possibility of clinically significant improvement favouring LABA/LAMA over LABA. Table 61 shows the rank statistics for the three treatment groups (sorted by mean rank). The highest ranked treatment group was LABA/LAMA with a median rank of 1 (95% CrI 1st to 2nd).

The random-class effects model assumes that treatment effects within a class or group can vary. Table 62 reports the mean difference of each individual intervention compared to formoterol 9 to 12 μg twice daily. Tiotropium 18 μg once daily, tiotropium 5 μg once daily, and all the interventions in the LABA/LAMA group (formoterol/glycopyrronium 9.6 μg/18 μg twice daily, indacaterol/glycopyrronium 27.5 μg/15.6 μg twice daily, indacaterol/glycopyrronium 110 μg/50 μg once daily, olodaterol/tiotropium 5 μg/5 μg once daily and formoterol/aclidinium 12 μg/400 μg twice daily) showed an increase in FEV1 at 12 months compared to formoterol 9 to 12 μg twice daily.

2.5.3.3 Pairwise meta-analyses

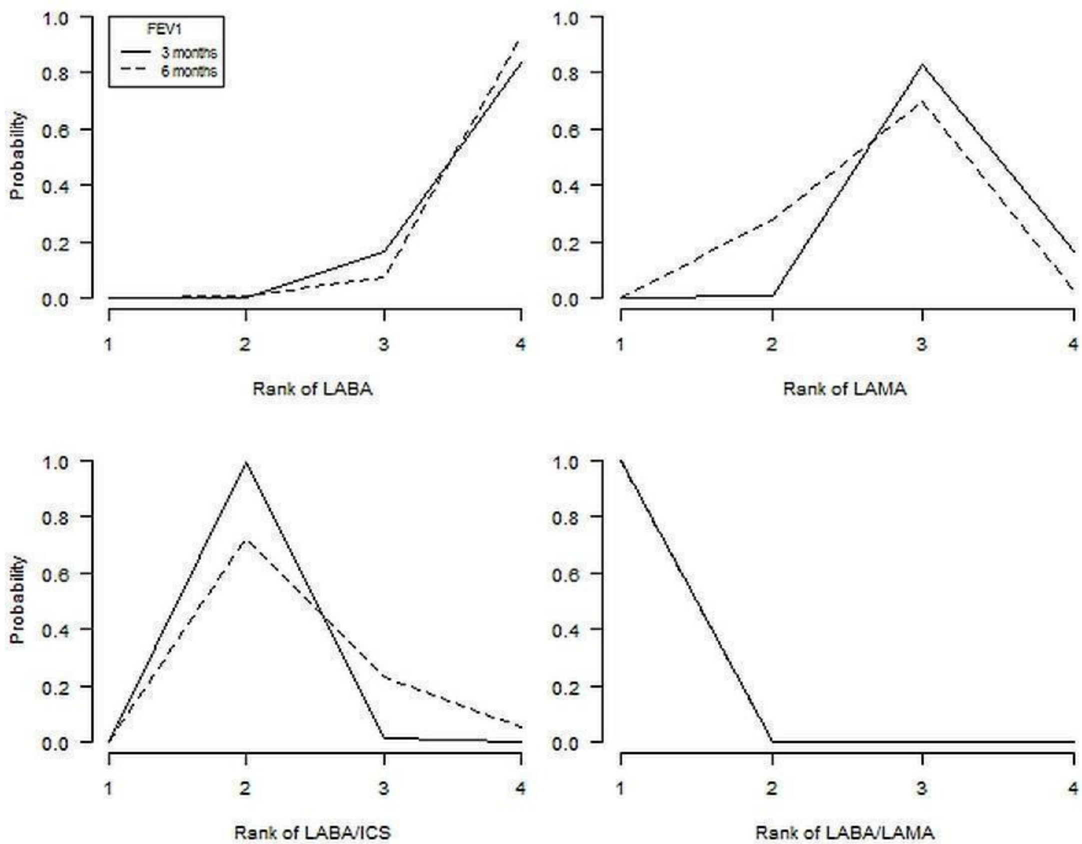
The results from pairwise MAs were consistent with the NMA (the random-treatment-effects model with fixed classes), except for LAMA versus LABA, in which there was a significant improvement with LAMA compared to LABA (MD 0.02, 95% CI 0.01 to 0.03; Appendix 7). However, there is no evidence that any treatment group is associated with clinically significant improvement (MCID of 0.1 L), compared to the others (very low-certainty evidence). Appendix 7 shows the certainty of evidence for the rest of the comparisons. There was no difference between random and fixed analyses.

2.5.4 Rank probabilities for change from baseline in FEV1

Figure 38 plots the ranks of each treatment group for FEV1 at three and six months only. We have not plotted ranks at 12 months, as only three treatment groups were available for comparison. The vertical axis shows the probability of being the best, second best, third best, or worst treatment group. LABA/LAMA has nearly 100% probability of being ranked first at three and six months, with LABA having a very high probability of being the worst intervention at three and six months.

Figure 38. Plot of rank probabilities for each treatment group in change in forced expiratory volume in 1 second in the low-risk population

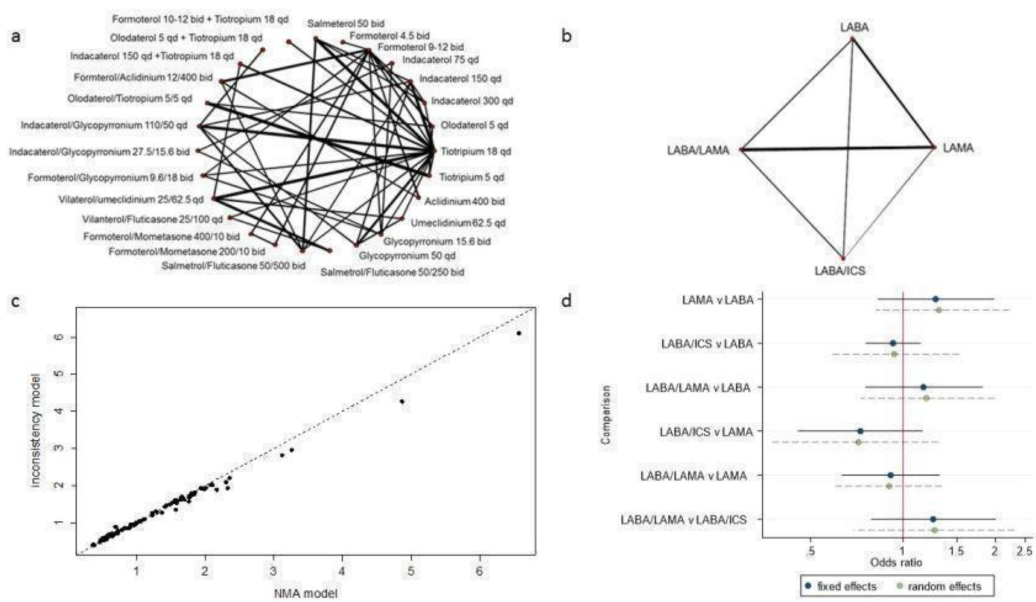
Change from baseline in forced expiratory volume in 1 second at 3 (solid line), and 6 months (dashed line). ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.6 Outcome: mortality

We included 51 studies of 27 interventions and four treatment groups for this outcome (Appendix 3; Figure 39 a and b).

Figure 39. Mortality in the low-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 1 favour the first named treatment group. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.6.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on a random-treatment-effects model with fixed-class effects for comparison. Results should be interpreted with some caution due to poor model fit, which can be attributed to studies with zero cells (Appendix 4).

2.6.2 NMA results

The NMA included a total of 56,493 participants (LABA: 11,488, LAMA: 25,324, LABA/ICS: 7586, LABA/LAMA: 12,095). The median duration of follow-up was 24 weeks (range 12 to 156 weeks). Figure 39d and Table 63 show the OR of mortality for each treatment group compared to every other. There was no evidence to suggest that any treatment group increased or decreased the odds of mortality compared to any other.

Table 64 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group was LABA/ICS with a median rank of 1 (95% CrI 1st to 4th), although the wide CrIs around the mean highlight the uncertainty in the results.

2.6.3 Pairwise meta-analyses

The results from pairwise MAs were consistent with the NMAs and there is no evidence to suggest that any treatment group increased or decreased the odds of mortality compared to any other (Appendix 7). The certainty of evidence was moderate for all comparisons. There was no difference between random and fixed analyses.

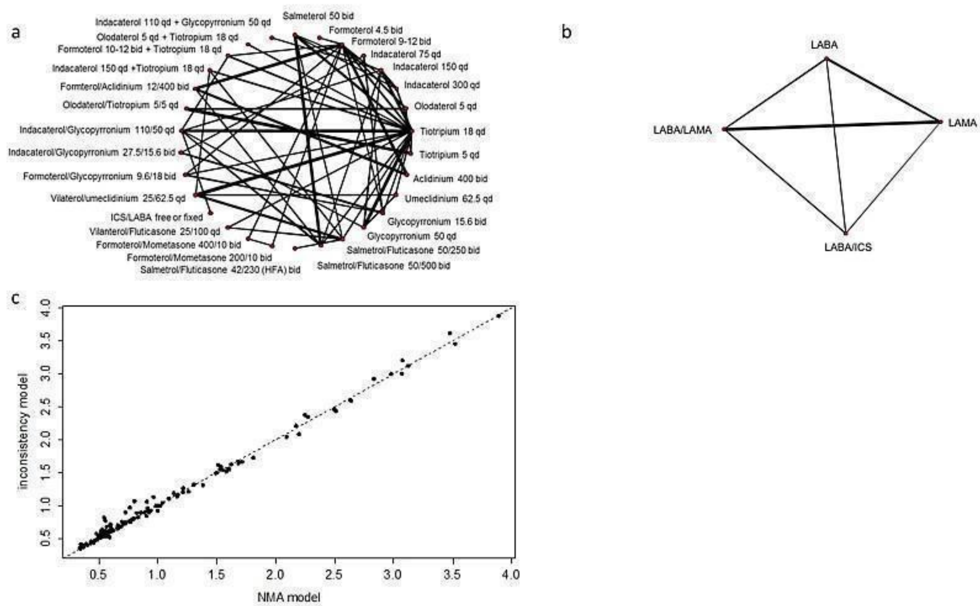
2.7 Outcome: serious adverse events (SAEs)

SAEs were separated into total SAEs, COPD SAEs and cardiac SAEs.

2.7.1 Outcome: total SAEs

The analysis for total SAEs included 67 studies of 30 interventions and four treatment groups. We included a total of 64,855 participants (LABA: 13,703, LAMA: 27,712, LABA/ICS: 8609, LABA/LAMA: 14,831; Appendix 3, Figure 40 a and b). The median duration of follow-up was 24 weeks (range 12 to 156 weeks).

Figure 40. Total serious adverse events in the low-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



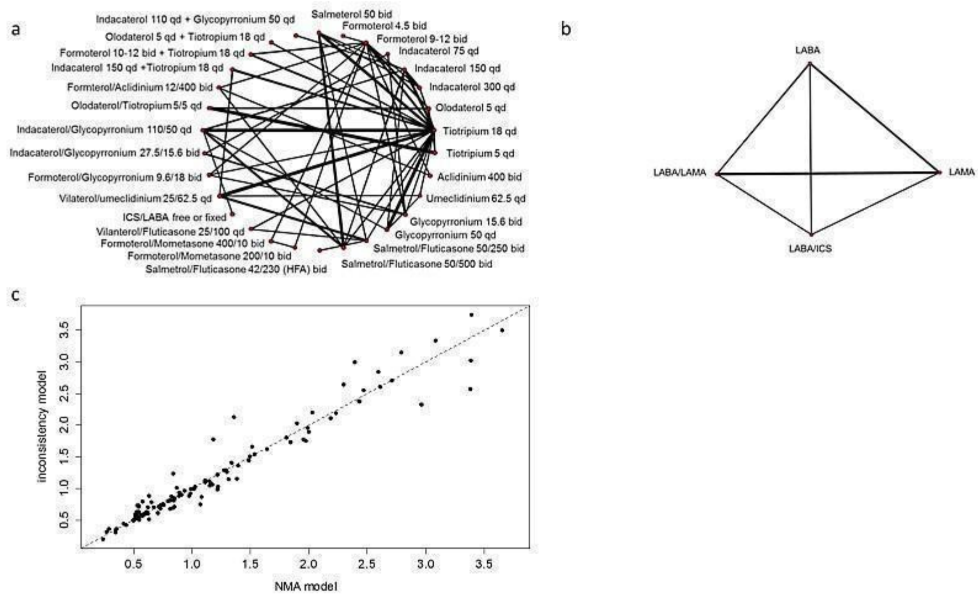
2.7.1.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on the random-treatment-effects model with fixed-class effects for comparison (Appendix 4).

2.7.2 Outcome: COPD SAEs

The analysis for COPD SAEs included 63 studies of 30 interventions and four treatment groups (Appendix 3; Figure 41 a and b). We included a total of 61,759 participants (LABA: 12,981, LAMA: 27,819, LABA/ICS: 7971, LABA/LAMA: 12,988)

Figure 41. Chronic obstructive pulmonary disease serious adverse events in the low-risk population a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



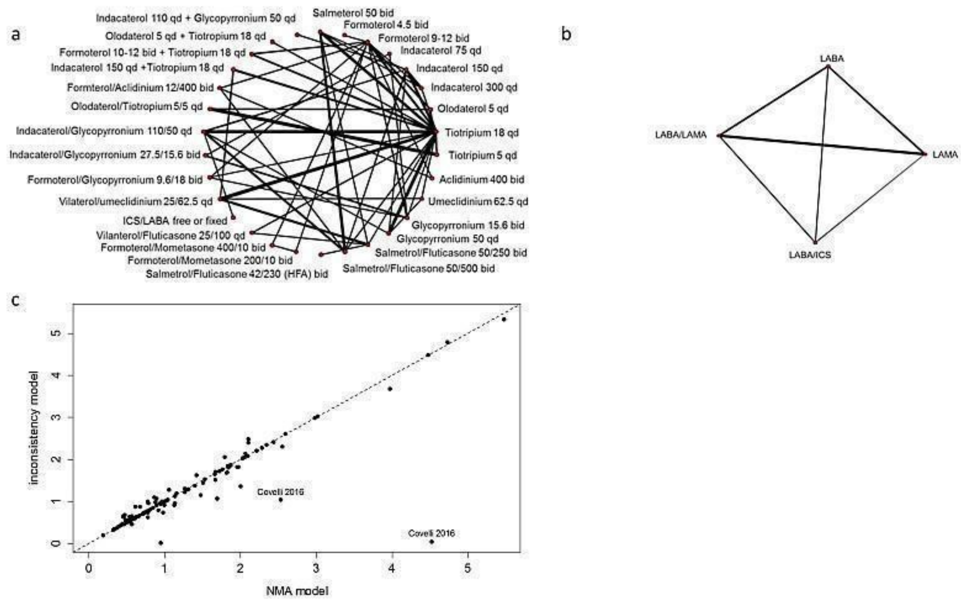
2.7.2.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on the random-treatment-effects model with fixed-class effects for comparison. Results should be interpreted with some caution due to poor model fit, which can be attributed to studies with zero cells (Appendix 4).

2.7.3 Outcome: cardiac SAEs

The analysis for cardiac SAEs included 58 studies of 29 interventions and four treatment groups (Appendix 3; Figure 42 a and b). We included a total of 62,007 participants (LABA: 12,581, LAMA: 24,747, LABA/ICS: 10,303, LABA/LAMA: 14,376).

Figure 42. Cardiac serious adverse events in the low-risk population
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.7.3.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on the random-treatment-effects model with fixed-class effects for comparison. Results should be interpreted with some caution due to poor model fit, which can be attributed to studies with zero cells.

2.7.4 NMA results

Table 65 shows the OR of each type of adverse event for each treatment group compared to every other. For total SAEs there was evidence of an increase in the odds of an event for LABA/ICS compared to LABA (OR 1.13, 95% CrI 1.01 to 1.27), although only if we used the fixed-effect model. For cardiac and COPD SAEs, there was no evidence that any treatment group increases or decreases the odds of an event compared to any other.

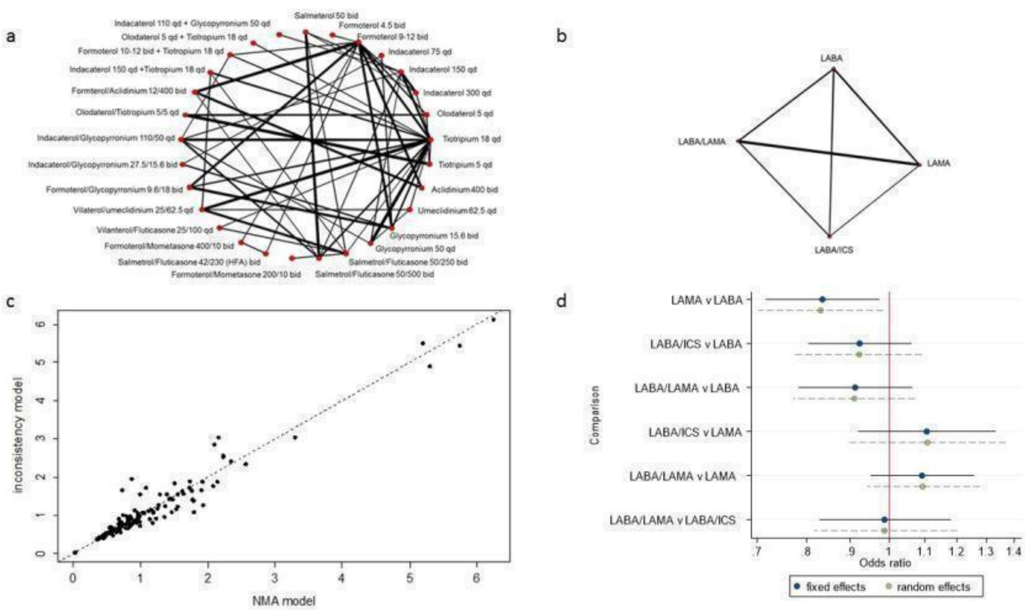
2.7.5 Pairwise meta-analyses

There is no evidence to suggest that any treatment group increases or decreases the odds of an event compared to the others with pairwise MAs. The results were consistent with the NMAs except for LABA/ICS versus LABA, in which LABA/ICS was associated with a significant increase in total SAEs compared to LABA with the fixed-effect NMA but not with the pairwise MAs or random-effects NMA (Appendix 7; Table 65). Table 66 shows the certainty of evidence for each treatment group compared to every other. There was no difference between random and fixed analyses.

2.8 Outcome: dropouts due to serious adverse events (SAEs)

We included 65 studies of 29 interventions and four treatment groups for this outcome (Appendix 3; Figure 43 a and b).

Figure 43. Dropouts due to adverse events in the low-risk population.
a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot; d: plot of relative effects. Values less than 1 favour the first named treatment group. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.8.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on the random-treatment-effects model with fixed-class effects for comparison. Results should be interpreted with some caution due to poor model fit (Appendix 4).

2.8.2 NMA results

The NMA included a total of 62,831 participants (LABA: 13,074, LAMA: 27,155, LABA/ICS: 8394, LABA/LAMA: 14,208). The median duration of follow-up was 24 weeks (range 12 to 156 weeks). Figure 43d and Table 67 show the OR of dropouts due to adverse events for each treatment group compared to every other. There was no evidence to suggest that any treatment group increased or decreased the odds of dropout compared to any other except for LAMA versus LABA (OR 0.84, 95% CrI 0.72 to 0.97). Table 68 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group was LAMA with a median rank of 1 (95% CrIs 1st to 3rd), although the wide CrIs around the mean highlight the uncertainty in the results.

2.8.3 Pairwise meta-analyses

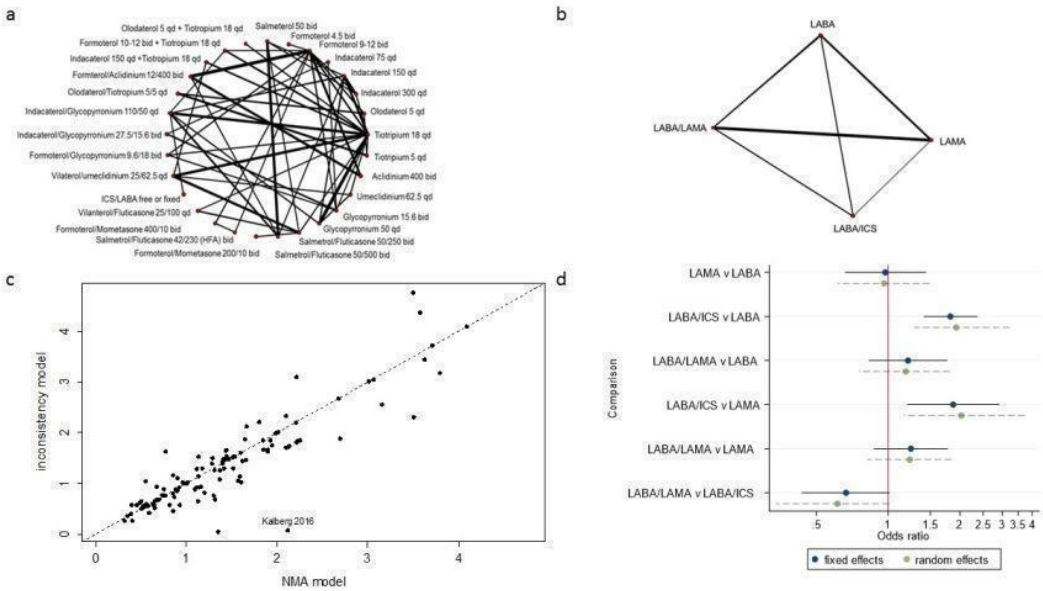
There is no evidence to suggest that any treatment group increases or decreases the odds of an event compared to the others with pairwise MAs. The results were consistent with the NMAs except for LAMA versus LABA, in which LAMA was associated with a significant decrease in dropouts due to adverse events compared to LABA in the NMA (OR 0.84, 95% CrI 0.72 to 0.97), but not in the pairwise MA (OR 0.90, 95% CI 0.73 to 1.10; Appendix 7). The certainty of evidence was moderate for LABA/ICS or LAMA versus LABA, low for LABA/LAMA versus LABA/ICS or LAMA and LABA/ICS versus LAMA, and very low for LABA/LAMA versus LABA. There was no difference between random and fixed analyses.

2.9 Outcome: pneumonia

We included 61 studies of 29 interventions and four treatment groups for this outcome (Appendix 3; Figure 44 a and b).

Figure 44. Pneumonia in the low-risk population

a: network diagram of interventions; b: network diagram of treatment groups; c: deviance plot (deviance points from the fixed-effect model with fixed-class effect and from the fixed-effect inconsistency model with fixed-class effect); d: plot of relative effects. Values less than 1 favour the first named treatment group. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist



2.9.1 Model selection and inconsistency checking

We chose a fixed-treatment-effect model with fixed-class effects, assuming consistency. We also report results based on a random-treatment-effects model with fixed-class effects and informative prior distribution on the heterogeneity parameter for comparison. Results should be interpreted with caution due to potential inconsistency in the data (Appendix 4).

2.9.2 NMA results

The NMA included a total of 61,157 participants (LABA: 12,640, LAMA: 26,596, LABA/ICS: 7518, LABA/LAMA: 14,403). The median duration of follow-up was 24 weeks (range 12 to 156 weeks). Figure 44d and Table 69 show the OR of pneumonia for each treatment group compared to every other. There is evidence to suggest that LABA/ICS increases the odds of pneumonia compared to LAMA and LABA (OR 2.02, 95% CrI 1.16 to 3.72; OR 1.93, 95% CrI 1.29 to 3.22), but no evidence of differences across other comparisons (Appendix 7; Summary of findings 7). Table 70 shows the rank statistics for the four treatment groups (sorted by mean rank). The highest ranked treatment group was LAMA with a median rank of 1 (95% CrI 1st to 3rd), although note the uncertainty in all the rankings.

2.9.3 Clinical homogeneity assessment

Table 6 shows the clinical homogeneity assessment across the available comparisons. Pre-bronchodilator baseline FEV1 ranged from 1.14 L to 1.34 L. The comparisons of LABA/ICS versus monotherapies had a lower baseline FEV1 compared with those of LABA/LAMA versus monotherapies, which could have introduced a bias against LABA/ICS. The NMA results should be interpreted with caution because of the difference in the baseline FEV1 across the pairwise comparisons.

2.9.4 Pairwise meta-analyses

The results from pairwise MAs suggest that LABA/ICS increases the odds of pneumonia compared to LABA/LAMA and LABA (OR 2.33, 95% CI 1.03 to 5.26; OR 1.64, 95% CI 1.25 to 2.14). The difference was significant for LABA/LAMA versus LABA/ICS with the pairwise MAs (moderate-certainty evidence), but not with the NMAs, and significant for LABA/ICS versus LAMA (OR 2.02, 95% CrI 1.16 to 3.72), with the NMA but not with the pairwise MA (OR 5.82, 95% CI 0.70 to 48.80; low-certainty evidence; Appendix 7). The certainty of evidence was high for LABA/ICS versus LABA, moderate for LABA/LAMA versus LAMA or LABA, and LAMA versus LABA (see 'Summary of findings' tables). The aforementioned difference in the baseline FEV1 across the pairwise comparisons may have affected the NMA results. There was no difference between random and fixed analyses.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

LABA/LAMA compared to LAMA for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease with predicted FEV1 of less than 80%
Setting: outpatient
Intervention: LABA/LAMA
Comparison: LAMA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with LAMA	Risk difference with LABA/LAMA			
Moderate to severe exacerbations: high-risk population	561 per 1000	14 more per 1000 (29 fewer to 58 more)	OR 1.06 (0.89 to 1.27)	2206 (1 RCT)	⊕⊕⊕○ Moderate[1,2,3]
Moderate to severe exacerbations: low-risk population	108 per 1000	7 fewer per 1000 (34 fewer to 28 more)	OR 0.93 (0.66 to 1.30)	5192 (8 RCTs)	⊕⊕○○ Low[2,3,4,5]
Severe exacerbations: high-risk population	397 per 1000	72 fewer per 1000 (169 fewer to 36 more)	OR 0.73 (0.45 to 1.16)	304 (1 RCT)	⊕⊕⊕○ Moderate[2,3]
Severe exacerbations: low-risk population	17 per 1000	0 fewer per 1000 (7 fewer to 12 more)	OR 0.99 (0.57 to 1.72)	4937 (7 RCTs)	⊕⊕⊕○ Moderate[2,3,4]
Pneumonia: high-risk population	30 per 1000	1 fewer per 1000 (12 fewer to 17 more)	OR 0.98 (0.59 to 1.61)	2510 (2 RCTs)	⊕⊕⊕○ Moderate[2,3,4]
Pneumonia: low-risk population	6 per 1000	1 more per 1000 (1 fewer to 4 more)	OR 1.23 (0.84 to 1.81)	18,538 (22 RCTs)	⊕⊕⊕○ Moderate[3,4,6]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FEV1**: forced expiratory volume-one second; **ICS**: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **OR:** odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Results were unchanged when open tiotropium arm was excluded.
[2] Optimal information size was not met.
[3] We could not exclude the possibility of a clinically important difference due to a wide 95% CI.
[4] Results were unchanged when studies with open tiotropium arm were excluded one by one or all together.
[5] Moderate heterogeneity (I^2 = 30% to 60%).
[6] Results were unchanged when studies with uneven and/or high dropouts were excluded one by one or all together.

LABA/LAMA compared to LABA for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease with predicted FEV1 of less than 80%
Setting: outpatient
Intervention: LABA/LAMA
Comparison: LABA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with LABA	Risk difference with LABA/LAMA			
Moderate to severe exacerbations: high-risk population	-	-	-	0 (0 RCTs)	-
Moderate to severe exacerbations: low-risk population	166 per 1000	33 fewer per 1000 (56 fewer to 4 fewer)	OR 0.77 (0.62 to 0.97)	2488 (5 RCTs)	⊕⊕⊕◯ Moderate[1]
Severe exacerbations: high-risk population	-	-	-	0 (0 RCTs)	-
Severe exacerbations: low-risk population	59 per 1000	12 fewer per 1000 (25 fewer to 7 more)	OR 0.78 (0.55 to 1.12)	2898 (6 RCTs)	⊕⊕⊕◯ Moderate[1,2]
Pneumonia: high-risk population	-	-	-	0 (0 RCTs)	-
Pneumonia: low-risk population	7 per 1000	4 more per 1000 (0 fewer to 10 more)	OR 1.54 (0.95 to 2.49)	8252 (10 RCTs)	⊕⊕⊕◯ Moderate[2]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FEV1**: forced expiratory volume-one second; **ICS**: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **OR:** odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Optimal information size was not met.
[2]A clinically important difference cannot be excluded due to a wide 95% CI.

LABA/ICS compared to LAMA for chronic obstructive pulmonary disease (COPD)

Patient or population: chronic obstructive pulmonary disease with predicted FEV1 of less than 80%
Setting: outpatient
Intervention: LABA/ICS
Comparison: LAMA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with LAMA	Risk difference with LABA/ICS			
Moderate to severe exacerbations: high-risk population	504 per 1000	28 more per 1000 (26 fewer to 81 more)	OR 1.12 (0.90 to 1.39)	1580 (2 RCTs)	⊕⊕⊕◯ Moderate[1,2]
Moderate to severe exacerbations: low-risk population	35 per 1000	13 fewer per 1000 (26 fewer to 22 more)	OR 0.63 (0.24 to 1.66)	623 (1 RCT)	⊕⊕◯◯ Low[1,3]
Severe exacerbations: high-risk population	112 per 1000	27 more per 1000 (5 fewer to 67 more)	OR 1.28 (0.95 to 1.73)	1580 (2 RCTs)	⊕⊕⊕◯ Moderate[1,2]
Severe exacerbations: low-risk population	3 per 1000	6 more per 1000 (2 fewer to 83 more)	OR 3.05 (0.32 to 29.47)	623 (1 RCT)	⊕⊕◯◯ Low[1,2]
Pneumonia: high-risk population	28 per 1000	21 more per 1000 (2 more to 52 more)	OR 1.80 (1.06 to 3.06)	1580 (2 RCTs)	⊕⊕⊕◯ Moderate[1]
Pneumonia: low-risk population	0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)	OR 5.82 (0.70 to 48.80)	885 (2 RCTs)	⊕⊕◯◯ Low[1,2,3]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FEV1**: forced expiratory volume-one second; **ICS**: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **OR:** odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Optimal information size was not met.
[2] We could not exclude the possibility of a clinically important difference due to a wide 95% CI.
[3] Significant small study effects are possible due to small sample sizes in the included studies.

LABA/ICS compared to LABA for chronic obstructive pulmonary disease (COPD): a network meta-analysis

Patient or population: chronic obstructive pulmonary disease with predicted FEV1 of less than 80%
Setting: outpatient
Intervention: LABA/ICS
Comparison: LABA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with LABA	Risk difference with LABA/ICS			
Moderate to severe exacerbations: high-risk population	430 per 1000	51 fewer per 1000 (69 fewer to 28 fewer)	OR 0.81 (0.75 to 0.89)	9041 (10 RCTs)	⊕⊕⊕⊕ High[1]
Moderate to severe exacerbations: low-risk population	454 per 1000	46 fewer per 1000 (86 fewer to 5 fewer)	OR 0.83 (0.70 to 0.98)	6689 (6 RCTs)	⊕⊕⊕◯ Moderate[2]
Severe exacerbations: high-risk population	94 per 1000	8 fewer per 1000 (23 fewer to 11 more)	OR 0.91 (0.74 to 1.13)	4216 (5 RCTs)	⊕⊕⊕◯ Moderate[1,3,4]
Severe exacerbations: low-risk population	130 per 1000	7 more per 1000 (11 fewer to 26 more)	OR 1.06 (0.90 to 1.24)	6482 (6 RCTs)	⊕⊕⊕⊕ High
Pneumonia: high-risk population	14 per 1000	6 more per 1000 (0 fewer to 15 more)	OR 1.46 (1.03 to 2.08)	12586 (14 RCTs)	⊕⊕⊕◯ Moderate[5]
Pneumonia: low-risk population	29 per 1000	18 more per 1000 (7 more to 31 more)	OR 1.64 (1.25 to 2.14)	6705 (6 RCTs)	⊕⊕⊕⊕ High

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FEV1**: forced expiratory volume-one second; **ICS**: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **OR:** odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Results were unchanged when we excluded studies with uneven dropouts, one by one or all together.
[2]Moderate heterogeneity (I^2 = 30% to 60%).
[3]Optimal information size not met.
[4] We could not exclude the possibility of a clinically important difference due to a wide 95% CI.
[5]Several studies had a high dropout rate and 95% CI crossed/uncrossed the line of no difference when we excluded a study with a high dropout rate.

LAMA compared to LABA for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease with predicted FEV1 of less than 80%
Setting: outpatient
Intervention: LAMA
Comparison: LABA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with LABA	Risk difference with LAMA			
Moderate to severe exacerbations: high-risk population	385 per 1000	40 fewer per 1000 (63 fewer to 20 fewer)	OR 0.84 (0.76 to 0.92)	7376 (1 RCT)	⊕⊕⊕⊕ High
Moderate to severe exacerbations: low-risk population	198 per 1000	13 fewer per 1000 (35 fewer to 11 more)	OR 0.92 (0.79 to 1.07)	4567 (5 RCTs)	⊕⊕⊕◯ Moderate[1,2]
Severe exacerbations: high-risk population	151 per 1000	16 fewer per 1000 (29 fewer to 1 more)	OR 0.88 (0.78 to 1.01)	7376 (1 RCT)	⊕⊕⊕◯ Moderate[2]
Severe exacerbations: low-risk population	30 per 1000	10 fewer per 1000 (19 fewer to 4 more)	OR 0.64 (0.36 to 1.13)	3320 (4 RCTs)	⊕⊕◯◯ Low[2,3,4]
Pneumonia: high-risk population	17 per 1000	3 fewer per 1000 (7 fewer to 2 more)	OR 0.83 (0.61 to 1.13)	10,815 (2 RCTs)	⊕⊕⊕◯ Moderate[4]
Pneumonia: low-risk population	7 per 1000	0 fewer per 1000 (3 fewer to 5 more)	OR 1.01 (0.61 to 1.69)	11,338 (10 RCTs)	⊕⊕⊕◯ Moderate[4]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FEV1**: forced expiratory volume-one second; **ICS**: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **OR:** odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Results were unchanged when we excluded studies with open-label tiotropium arm, one by one or all together.
[2] Optimal information size was not met.
[3] 95% CI no longer contained the line of no difference when we excluded a study with open-label tiotropium arm.
[4] A clinically important difference cannot be excluded due to a wide 95% CI.

Patient or population: chronic obstructive pulmonary disease with predicted FEV1 of less than 80%
Settings: outpatient

Outcomes	Anticipated absolute effects* (95% CrI)		Relative effect (95% CrI)	No of participants (studies)
	Risk with LABA	Risk difference with LABA/LAMA		
Moderate to severe exacerbations: high-risk population	427 per 1000	106 fewer per 1000 (139 fewer to 68 fewer)	HR 0.70 (0.61 to 0.80)	11,113 (21 RCTs)
Moderate to severe exacerbations: low-risk population	250 per 1000	52 fewer per 1000 (76 fewer to 25 more)	HR 0.78 (0.67 to 0.90)	14,450 (28 RCTs)
Severe exacerbations: high-risk population	142 per 1000	48 fewer per 1000 (66 fewer to 26 fewer)	HR 0.64 (0.51 to 0.81)	9,045 (13 RCTs)
Severe exacerbations: low-risk population	92 per 1000	24 fewer per 1000 (44 fewer to 2 more)	HR 0.72 (0.48 to 1.02)	11,127 (31 RCTs)
	Risk with LABA	**Risk difference with LABA/ICS**	**Relative effect (95% CrI)**	**No of participants (studies)**
Moderate to severe exacerbations: high-risk population	427 per 1000	66 fewer per 1000 (87 fewer to 46 fewer)	HR 0.80 (0.75 to 0.86)	18,561 (21 RCTs)
Moderate to severe exacerbations: low-risk population	250 per 1000	24 fewer per 1000 (37 fewer to 10 fewer)	HR 0.89 (0.84 to 0.96)	16,437 (28 RCTs)
Severe exacerbations: high-risk population	142 per 1000	23 fewer per 1000 (39 fewer to 4 fewer)	HR 0.83 (0.71 to 0.97)	12,447 (13 RCTs)
Severe exacerbations: low-risk population	92 per 1000	2 more per 1000 (10 fewer to 15 more)	HR 1.01 (0.72 to 1.28)	12,265 (31 RCTs)

	Risk with LABA	**Risk difference with LAMA**	**Relative effect (95% CrI)**	**No of participants (studies)**
Moderate to severe exacerbations: high-risk population	427 per 1000	69 fewer per 1000 (99 fewer to 40 fewer)	HR 0.80 (0.71 to 0.88)	16,655 (21 RCTs)
Moderate to severe exacerbations: low-risk population	250 per 1000	27 fewer per 1000 (48 fewer to 5 fewer)	HR 0.87 (0.78 to 0.97)	14,209 (28 RCTs)
Severe exacerbations: high-risk population	142 per 1000	37 fewer per 1000 (49 fewer to 24 fewer)	HR 0.72 (0.63 to 0.82)	15,205 (13 RCTs)
Severe exacerbations: low-risk population	92 per 1000	15 fewer per 1000 (29 fewer to 2 more)	HR HR 0.80 (0.56 to 1.05)	22,819 (31 RCTs)
	Risk with LABA/ICS	**Risk difference with LABA/LAMA**	**Relative effect (95% CrI)**	**No of participants (studies)**
Pneumonia: high-risk population	24 per 1000	10 fewer per 1000 (14 fewer to 4 fewer)	OR 1.69 (1.2 to 2.44)	13,546 (24 RCTs)
Pneumonia: low-risk population	24 per 1000	8 fewer per 1000 (13 fewer to 0 fewer)	OR 1.64 (0.99 to 2.94)	27,043 (61 RCTs)
	Risk with LABA/ICS	**Risk difference with LAMA**	**Relative effect (95% CrI)**	**No of participants (studies)**
Pneumonia: high-risk population	24 per 1000	10 fewer per 1000 (14 fewer to 6 fewer)	OR 1.78 (1.33 to 2.39)	18,844 (24 RCTs)
Pneumonia: low-risk population	24 per 1000	11 fewer per 1000 (16 fewer to 4 fewer)	OR 2.02 (1.16 to 3.72)	39,236 (31 RCTs)
	Risk with LABA/ICS	**Risk difference with LABA**	**Relative effect (95% CrI)**	**No of participants (studies)**

Pneumonia: high-risk population	24 per 1000	8 fewer per 1000 (11 fewer to 3 fewer)	OR 1.50 (1.17 to 1.92)	21,404 (24 RCTs)
Pneumonia: low-risk population	24 per 1000	11 fewer per 1000 (14 fewer to 7 fewer)	OR 1.93 (1.29 to 3.22)	20,158 (61 RCTs)

***The risk in the intervention group** (and its 95% credible interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CrI).
CrI: credible interval; **FEV1**: forced expiratory volume-one second; **HR**: hazard ratio; **ICS**: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **OR:** odds ratio; **RCT:** randomised controlled trial

DISCUSSION

Summary of main results

We assumed a class/group effect in all treatment groups because the random-class-effects model did not significantly improve model fit compared to the fixed-class-effects model except for change from baseline in FEV1 at 12 months in the low-risk population, which argues against intraclass/group differences in any of the treatment groups we analysed. We have summarised the results in Appendix 6, Appendix 7, and Appendix 5.

The NMAs suggested that LABA/LAMA combination was the highest ranked treatment group to reduce moderate to severe and severe exacerbations, followed by LAMA. There is evidence that LABA/LAMA significantly reduces moderate to severe exacerbations compared to all others, and severe exacerbations compared to LABA/ICS and LABA in the high-risk population.

The LABA/ICS combination was ranked third for moderate to severe exacerbations and severe exacerbations in the high-risk population and ranked fourth for the severe exacerbations in the low-risk population. LABA was the worst ranked, except for severe exacerbations in the low-risk population, for which they were ranked third.

In the pairwise MAs, there was no definite evidence that LABA/LAMA or LAMA reduced moderate to severe or severe exacerbations compared to LABA/ICS in both populations, although a clinically meaningful reduction could not be excluded due to a wide 95% CI.

With regard to symptom and quality-of-life scores, the combination therapies, LABA/LAMA and LABA/ICS were generally ranked higher than monotherapies in both populations. LAMA/LABA was ranked higher than LABA/ICS in the high-risk population. There were significant overlaps in the rank statistics between LABA/LAMA and LABA/ICS as well as between LAMA and LABA in the low-risk population.

In the high-risk population of pairwise MAs, the LABA/LAMA combination significantly increased SGRQ responders compared to LAMA at six months, LABA/ICS at 12 months, and LAMA at 12 months (Appendix 6).

In the low-risk population of pairwise MAs, the LABA/LAMA combination significantly increased SGRQ responders compared to LAMA at three and six months and LABA at six months (Appendix 7).

The LABA/ICS combination significantly increased SGRQ responders compared to LABA at 12 months and the odds ratio of SGRQ response was significantly lower with LAMA compared to LABA at three months. Otherwise, none of the differences in symptom and quality-of-life scores met the MCID criteria of clinical significance in either high- or low-risk populations.

The LABA/ICS combination was the lowest ranked in pneumonia SAEs in the high- and low-risk populations. In the high-risk population, LABA/ICS significantly increased the odds of pneumonia compared to LAMA/LABA, LAMA, and LABA both in the NMA and pairwise MAs. In the low-risk population, LABA/ICS increased the odds of pneumonia compared to LAMA and LABA in the NMA and compared to LABA/LAMA and LABA in the pairwise MAs.

There were significant overlaps in the rank statistics in the other safety outcomes. LABA/ICS significantly increased total SAEs compared to LABA, and LAMA significantly reduced COPD SAEs compared to LABA, both in the NMAs and pairwise MAs. In the low-risk population, LABA/ICS significantly increased total SAEs and LAMA significantly reduced dropouts due to adverse events compared to LABA in the NMAs but not in the pairwise MAs. Otherwise, there was no evidence to suggest that any treatment group increased the odds of SAEs or dropout compared to the others.

With regard to pre-bronchodilator FEV1, the highest ranked treatment group was LABA/LAMA with a median rank of 1 whereas LABA was the worst ranked with a median of 4 at all time points. LABA/ICS and LAMA were ranked second or third. In the pairwise MAs, a significant difference was seen in some comparisons but the 95% CIs crossed the line of MCID of 0.1 L, suggesting none of the differences was clinically meaningful.

Overall completeness and applicability of evidence

The study results are not applicable to those with a milder form of COPD because people with mild COPD do not usually require a maintenance inhaler therapy and we did not include them in our analysis.

We also excluded people with asthma, although the baseline bronchodilator response was quite significant in some studies despite the exclusion (Table 1). It is unclear whether efficacies of ICS/LABA would be different in people without a history of asthma but with a significant bronchodilator response, which is usually seen in a more severe form of the disease. Cardiac SAEs could have been underestimated due to the exclusion of people with a significant cardiovascular comorbidity in a majority of included studies.

We excluded drug formulations or doses that were not approved or available for clinical use, as well as nebulised medications. Therefore, the results are not applicable for nebulised or off-label use of available medications.

Otherwise, we included a total of 101,311 participants from 99 studies from across the world to be as comprehensive as possible. We used a Bayesian shared parameter model for COPD exacerbations and were able to avoid losing a substantial amount of relevant data (e.g. 6 out of 13 studies in severe exacerbations in the high-risk population). We were able to collect a substantial amount of data from manufacturers' websites and ClinicalTrials.gov due to greater transparency from pharmaceutical companies.

Quality of the evidence

All included studies were RCTs, and the quality of included RCTs was generally good (Figure 2). Nineteen studies had an open tiotropium arm and 16 studies had relatively uneven dropouts. The results were unchanged in most of comparisons when we excluded those studies one by one or all together in the pairwise analyses. Otherwise, we downgraded the certainty rating by one or even two levels in some comparisons.

We had a total of 189 head-to-head comparisons in the pairwise MAs and the certainty of evidence was high, moderate, low and very low in 40, 99, 39, and 11 comparisons respectively. The primary reason for downgrading was a suboptimal information size or a wide 95% CI. Our confidence in the findings increased when the NMAs supported the pairwise results with a much greater information size. The results should be interpreted with caution for those derived from a small sample size or with low or very low certainty of evidence, or both (see 'Summary of findings' tables; Appendix 6; Appendix 7).

We found no evidence of inconsistency or effect modifiers when we compared the model fit and between-study heterogeneity from NMA models with those from an unrelated effects (inconsistency) model except for mortality in the high-risk population, as well as in change from baseline in FEV1 at six months, cardiac SAEs, and pneumonia in the low-risk population.

The results from the NMAs and pairwise MAs were consistent, which would make significant inconsistency less likely except for pneumonia in the low-risk population (Appendix 6; Appendix 7). The mean baseline FEV1 of between-treatment group comparisons for pneumonia in the low-risk population, ranged from 1.14 L to 1.34 L (Table 6), which could be a potential effect modifier and possibly explain the inconsistency in this outcome. Therefore the NMA results of this outcome should be interpreted cautiously and in relation to the results from direct comparisons.

Potential biases in the review process

Incorporating indirect comparisons increases information size and statistical power. However it could introduce bias if there is a difference in participants, co-interventions, or trial methodology between contrasts in a network (intransitivity), which is an inherent issue to a NMA. We took several measures to assess and minimise intransitivity.

1. We reviewed the study population after the first draft of our protocol and divided the entire population into high- and low-risk populations because we thought such differences in the study population could introduce intransitivity. We acknowledge that blood eosinophil counts could be an effect modifier for LABA/ICS but available data were insufficient to include them as a covariate as a way of exploring subgroup effects.
2. We constructed summary tables organised by treatment group pair-wise comparisons (Table 2; Table 3; Table 4; Table 5; Table 6), for the primary outcomes in both populations and also in pneumonia in the low-risk population to assess clinical and methodological similarities/dissimilarities of the studies.
3. We performed NMAs and pairwise MAs to address possible intransitivity when there was a discrepancy between them (Appendix 6; Appendix 7).
4. We analysed several outcomes at different time points (e.g. 3, 6, and 12 months), when feasible.
5. We assessed consistency using the inconsistency models, acknowledged a possibility of intransitivity when suspected, and interpreted the results accordingly.

Agreements and disagreements with other studies or reviews

There are an increasing number of systematic reviews comparing LAMA/LABA with existing maintenance inhalers (Farne 2015; Oba 2016a; Oba 2016b). Our results are essentially similar to the existing reports but there are some differences in data collection and interpretations of the results.

Chen 2017 concluded that, "LAMA were associated with a greater reduction in acute exacerbations and fewer adverse effects compared with LABA." They analysed all severities of exacerbation (mild, moderate, and severe), and adverse event (serious and non-serious), including vilanterol, which was not approved or available for clinical use whereas our study analysed moderate to severe and severe exacerbations and SAEs (i.e. serious only), excluding vilanterol, which would be of greater clinical relevance in our opinion.

Horita 2017 reported "LAMA+LABA has fewer exacerbations… And more frequent improvement in quality of life as measured by an increase over 4 units or more of the SGRQ" compared to LABA/ICS. They included all severities of COPD exacerbation and analysed SGRQ responders at all time points combined together whereas we separated out moderate to severe and severe exacerbations and assessed SGRQ responders at different time points because previous reports suggested that a proportion of SGRQ responders changed over time after study entry.

Kew 2014 compared LABA/ICS, LAMA, LABA, and placebo, and concluded, "Quality of life and lung function were improved most on combination inhalers (LABA and ICS) and least on ICS alone at 6 and at 12 months." We did not include ICS because it is now not commonly used as monotherapy in COPD and emphasised clinical significance/insignificance of the reported differences based on the recommended MCIDs.

Rodrigo 2017 concluded "The greater efficacy and comparable safety profiles observed with LABA/LAMA combinations versus LAMA or LABA/ICS" and "LABA/LAMA significantly reduced moderate/severe exacerbation rate compared with LABA/ICS", which was based on two studies. Our pairwise analyses included seven studies for moderate to severe exacerbations (one in the high-risk and six in the low-risk populations) and five studies for severe exacerbations (one in the high-risk and four in the low-risk populations). In addition, we performed NMAs with much greater statistical power and addressed uncertainty surrounding these outcomes, taking effect modifiers into consideration. Schlueter 2016 concluded "All LAMA/LABA FDCs were found to have similar efficacy and safety", which agrees with our results. We examined a class/group effect not only in LABA/LAMA combinations but also in LABA/ICS combinations, LAMAs, and LABAs. Welsh 2013 compared LABA/ICS versus tiotropium (LAMA), and concluded, "The relative efficacy and safety of combined inhalers and tiotropium remains uncertain" because of missing outcome data. We examined the proportion of missing data in each outcome, which varied widely, and downgraded the certainty of evidence accordingly.

AUTHORS' CONCLUSIONS

Implications for practice

In conclusion, long-acting β-agonist/long-acting muscarinic antagonist (LABA/LAMA), may have an advantage over LABA/inhaled corticosteroid (ICS), to reduce chronic obstructive pulmonary disease (COPD), exacerbations in the high-risk population and over monotherapies to improve participant-reported outcomes, such as symptoms and perceived health status, in people with or without a history of COPD exacerbations. LAMA may be preferred over LABA to reduce COPD exacerbations, especially in the high-risk population. ICS-containing inhalers are associated with an increased risk of pneumonia.

Implications for research

The efficacy of maintenance inhaler therapies appears modest at best. Research and development of a new therapy, such as triple combination therapy, which would have a greater impact on controlling symptoms and preventing exacerbations, are much desired. Meanwhile further investigation on how best to use the existing inhaler therapies in subgroups of patients, such as in those with blood eosinophilia and varying degrees of bronchial reactivity would be helpful. There is a need for more studies evaluating COPD subpopulations or phenotypes.

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REFERENCES

References to studies included in this review

Aaron 2007 ***{published and unpublished data}***
Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease. *Annals of Internal Medicine* 2007;**146**(8):545–55. PUBMED: 17310045]

Agusti 2014 ***{published and unpublished data}***
* Agustí A, de Teresa L, De Backer W, Zvarich MT, Locantore N, Barnes N, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. *European Respiratory Journal* 2014;**43**(3):763–72. PUBMED: 24114969]
GSK113107. A 12-week study to evaluate the 24 hour pulmonary function of fluticasone furoate (FF)/vilanterol inhalation powder (FF/VI inhalation powder) once daily compared with salmeterol/fluticasone propionate (FP) inhalation powder twice daily in subjects with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/gsk-113107-clinical-study-report-redact-v02.pdf (first received 9 February 2011).

Anzueto 2009 ***{published and unpublished data}***
* Anzueto A, Ferguson GT, Feldman G, Chinsky K, Seibert A, Emmett A, et al. Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. *COPD* 2009;**6**(5):320–9. PUBMED: 19863361]
GSK100250. A randomized, double-blind, parallel group, 52-week study to compare the effect of fluticasone propionate/salmeterol Diskus combination product 250/50mcg bid with salmeterol diskus 50mcg bid on the annual rate of moderate/severe exacerbations in subjects with chronic obstructive pulmonary disease. www.gsk-

clinicalstudyregister.com/files2/gsk-sco100250-clinical-study-report-redact.pdf (first received 27 December 2004).

Asai 2013 ***{published and unpublished data}***
Asai K, Minakata Y, Hirata K, Fukuchi Y, Kitawaki T, Ikeda K, et al. QVA149 once-daily is safe and well tolerated and improves lung function and health status in Japanese patients with COPD: the ARISE study. European Respiratory Society 23rd Annual Congress; 2013 September 7-11; Barcelona. 2013; Vol. A2223.

Bateman 2013 ***{published and unpublished data}***
Bateman ED, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. *European Respiratory Journal* 2013;**42**(6):1484–94. PUBMED: 23722616]

BI 205.137 2001 ***{unpublished data only}***
* BI 205.137. A multiple dose comparison of tiotropium inhalation capsules, salmeterol inhalation aerosol and placebo in a six-month, double-blind, double-dummy, safety and efficacy study in patients with chronic obstructive pulmonary disease (COPD). trials.boehringer-ingelheim.com/public/trial_results_documents/205/205.137_U01-1231-02.pdf (first received 21 February 2001).

Bogdan 2011 ***{published and unpublished data}***
Bogdan MA, Aizawa H, Fukuchi Y, Mishima M, Nishimura M, Ichinose M. Efficacy and safety of inhaled formoterol 4.5 and 9 μg twice daily in Japanese and European COPD patients: phase III study results. *BMC Pulmonary Medicine* 2011;**11**:51. PUBMED: 22085439]

Briggs 2005 ***{published and unpublished data}***
Boehringer Ingelheim International. A multiple dose comparison of tiotropium inhalation capsules and salmeterol inhalation aerosol in a 12 week, randomized, double-blind, double-dummy, parallel group study in patients with chronic obstructive pulmonary disease (COPD). trials.boehringer-ingelheim.com/public/trial_results_documents/205/205.264_CO.pdf 03 FEB 2004. ClinicalTrials.gov: NCT00274560]
* Briggs DD Jr, Covelli H, Lapidus R, Bhattycharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. *Pulmonary Pharmacology and Therapeutics* 2005;**18**(6):397–404. PUBMED: 16179215]
Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012, Issue 9. DOI: 10.1002/14651858.CD009157

Brusasco 2003 ***{published and unpublished data}***
* Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003;**58**(5):399–404. PUBMED: 12728159]
Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012, Issue 9. DOI: 10.1002/14651858.CD009157
Donohue JF, Menjoge S, Kesten S. Tolerance to bronchodilating effects of salmeterol in COPD. *Respiratory Medicine* 2003;**97**(9):1014–20. PUBMED: 14509555]
Donohue JF, Van Noord JA, Bateman ED, Langley SJ, Lee A, Witek TJ Jr, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002;**122**(1):47–55. PUBMED: 12114338]
Hodder R, Kesten S, Menjoge S, Viel K. Outcomes in COPD patients receiving tiotropium or salmeterol plus treatment with inhaled corticosteroids. *International Journal of Chronic Obstructive Pulmonary Disease* 2007;**2**(2):157–67. PUBMED: 18044688]

Buhl 2011 ***{published and unpublished data}***
Buhl R, Dunn LJ, Disdier C, Lassen C, Amos C, Henley M. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. *European Respiratory Journal* 2011;**38**(4):797–803. PUBMED: 21622587]

Buhl 2015a ***{published and unpublished data}***
Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). *European Respiratory Journal* 2015;**45**(4):969–79.

Buhl 2015a&b ***{published and unpublished data}***
Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). *European Respiratory Journal* 2015;**45**(4):969–79. PUBMED: 25573406]

Buhl 2015b ***{published and unpublished data}***
Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). *European Respiratory Journal* 2015;**45**(4):969–79.

Buhl 2015c ***{published and unpublished data}***
Buhl R, Gessner C, Schuermann W, Foerster K, Sieder C, Hiltl S, et al. Efficacy and safety of once-daily QVA149 compared with the free combination of once-daily tiotropium plus twice-daily formoterol in patients with moderate-to-severe COPD (QUANTIFY): a randomised, non-inferiority study. *Thorax* 2015;**70**(4):311–9. PUBMED: 25677679]

Calverley 2003 ***{published and unpublished data}***
Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *European Respiratory Journal* 2003;**22**(6):912–9. PUBMED: 14680078]

Calverley 2003 TRISTAN ***{published and unpublished data}***
* Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a

randomised controlled trial. *Lancet* 2003;**361**(9356): 449–56. PUBMED: 12583942]
GSK FCB3024 (Phase III). A multicentre, randomised, double-blind, parallel group study to compare the efficacy and safety of the salmeterol/fluticasone combination product (50/500mg strength) twice daily with salmeterol 50mg twice daily alone and fluticasone propionate 500mg twice daily alone, all delivered via the Diskus/Accuhaler inhaler, in the treatment of patients with chronic obstructive pulmonary disease. www.gsk-clinicalstudyregister.com/files2/sfcb3024-clinical-study-report-redact-v02.pdf (first received 20 August 1998).

Calverley 2007 ***{published and unpublished data}***
* Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *New England Journal of Medicine* 2007;**356**(8):775–89. PUBMED: 17314337]
GSKSCO30003. A multicentre, randomised, double-blind, parallel group, placebo-controlled study to investigate the long-term effects of salmeterol/fluticasone propionate (Seretide) 50/500mcg BD, salmeterol 50mcg BD and fluticasone propionate 500mcg BD, all delivered via the Diskus tm/Accuhaler tm inhaler, on mortality and morbidity of subjects with chronic obstructive pulmonary disease (COPD) over 3 years of treatment. www.gsk-clinicalstudyregister.com/files2/gsk-sco30003-clinical-study-report-redact-v03.pdf (first received 7 September 2000).

Calverley 2010 ***{published and unpublished data}***
Calverley PM, Kuna P, Monsó E, Costantini M, Petruzzelli S, Sergio F, et al. Beclomethasone/formoterol in the management of COPD: a randomised controlled trial. *Respiratory Medicine* 2010;**104**(12):1858–68. PUBMED: 20965712]

Cazzola 2007 ***{published and unpublished data}***
Cazzola M, Andò F, Santus P, Ruggeri P, Di Marco F, Sanduzzi A, et al. A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. *Pulmonary Pharmacology & Therapeutics* 2007;**20**(5):556–61. PUBMED: 16914336]

Chapman 2014 ***{published and unpublished data}***
Chapman KR, Beeh KM, Beier J, Bateman ED, D'Urzo A, Nutbrown R. A blinded evaluation of the efficacy and safety of glycopyrronium, a once-daily long-acting muscarinic antagonist, versus tiotropium, in patients with COPD: the GLOW5 study. *BMC Pulmonary Medicine* 2014;**17**(14):4. PUBMED: 24438744]

COMBINE 2017 ***{unpublished data only}***
NCT02055352. 24-week study to evaluate efficacy and safety of the combination budesonide /indacaterol vs fluticasone /salmeterol in patients with COPD (COMBINE). clinicaltrials.gov/ct2/show/NCT02055352 (first received 5 February 2014).

COSMOS-J 2016 ***{unpublished data only}***
* NCT01762800. Evaluating the control of COPD symptoms in patients treated with tiotropium bromide 18mcg once daily alone, ADOAIR 50/250mcg twice daily alone or ADOAIR 50/250mcg plus tiotropium bromide 18mcg. clinicaltrials.gov/ct2/show/NCT01762800 (first received 8 January 2013).

Covelli 2016 ***{published and unpublished data}***
* Covelli H, Pek B, Schenkenberger I, Scott-Wilson C, Emmett A, Crim C. Efficacy and safety of fluticasone furoate/vilanterol or tiotropium in subjects with COPD at cardiovascular risk. *International Journal of Chronic Obstructive Pulmonary Disease* 2015;**18**(11):1–12. PUBMED: 26730183]
GSK 115805. A 12-week study to evaluate the 24-hour pulmonary function profile of fluticasone furoate/vilanterol (FF/VI) inhalation powder 100/25mcg once-daily via a novel dry powder inhaler compared with tiotropium bromide inhalation powder 18mcg delivered once-daily via the HandiHaler in subjects with chronic obstructive pulmonary disease (COPD) who have or are at risk for co-morbid cardiovascular disease. gsk-clinicalstudyregister.com/files2/gsk-115805-clinical-study-report-redact.pdf (first received 2 April 2012).

D'Urzo 2014 ***{published and unpublished data}***
* D'Urzo AD, Rennard SI, Kerwin EM, Mergel V, Leselbaum AR, Caracta CF, et al. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. *Respiratory Research* 2014;**15**: 123. PUBMED: 25756831]
European Medicines Agency. Assessment report - Duaklir Genuair (aclidinium bromide/ formoterol fumarate dihydrate). www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003745/WC500178415.pdf (accessed prior to 15 August 2018).
The Federal Joint Committee (G-BA) in Germany. Resolution by the Federal Joint Committee on an amendment to the Pharmaceutical Directive (AM-RL): Appendix XII - Resolutions on the benefit assessment of pharmaceuticals with new active ingredients, in accordance with the German Social Code, Book Five (SGB V), section 35a aclidinium bromide/formoterol. www.english.g-ba.de/downloads/91-1028-156/Aclidinium%20bromide_formoterol_en.pdf (accessed prior to 15 August 2018).

D'Urzo 2017 ***{published and unpublished data}***
D'Urzo A, Rennard S, Kerwin E, Donohue JF, Lei A, Molins E. A randomised double-blind, placebo-controlled, long-term extension study of the efficacy, safety and tolerability of fixed-dose combinations of aclidinium/formoterol or monotherapy in the treatment of chronic obstructive pulmonary disease. *Respiratory Medicine* 2017;**125**:39–48. PUBMED: 28340861]

Dahl 2010 ***{published and unpublished data}***
Dahl R, Chung KF, Buhl R, Magnussen H, Nonikov V, Jack D, et al. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. *Thorax* 2010;**65**(6):473–9. PUBMED: 20522841]

Decramer 2013 ***{published and unpublished data}***
Decramer ML, Chapman KR, Dahl R, Frith P, Devouassoux G, Fritscher C, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. *Lancet Respiratory Medicine* 2013;**1**(7):524–33. PUBMED: 24461613]

Decramer 2014a ***{published and unpublished data}***
Decramer M, Anzueto A, Kerwin E, Kaelin T, Richard N, Crater G, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respiratory Medicine* 2014;**2**(6):472–86. PUBMED: 24835833]
GSk113360. A multicenter trial comparing the efficacy and safety of GSK573719/GW642444 with GW642444 and with tiotropium over 24 weeks in subjects with COPD. www.gsk-clinicalstudyregister.com/files2/gsk-113360-clinical-study-report-redact-v02.pdf (first received 21 March 2011).

Decramer 2014b ***{published and unpublished data}***
Decramer M, Anzueto A, Kerwin E, Kaelin T, Richard N, Crater G, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respiratory Medicine* 2014;**2**(6):472–86. PUBMED: 24835833]
* GSK113374. A multi-center trial comparing the efficacy and safety of GSK573719/GW642444 with GSK573719 and with tiotropium over 24 weeks in subjects with COPD. www.gsk-clinicalstudyregister.com/files2/gsk-113374-clinical-study-report-redact-v02.pdf (first received 21 March 2011).

Donohue 2010 ***{published and unpublished data}***
Barnes PJ, Pocock SJ, Magnussen H, Iqbal A, Kramer B, Higgins M, et al. Integrating indacaterol dose selection in a clinical study in COPD using an adaptive seamless design. *Pulmonary Pharmacology & Therapeutics* 2010;**3**:165–71. ClinicalTrials.gov: NCT00463567; PUBMED: 20080201]
* Donohue JF, Fogarty C, Lötvall J, Mahler DA, Worth H, Yorgancioglu A, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. *American Journal of Respiratory and Critical Care Medicine* 2010;**182**(2):155–62. PUBMED: 20463178]

Donohue 2013 ***{published and unpublished data}***
* Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respiratory Medicine* 2013;**107**(10):1538–46. PUBMED: 23830094]
GSK113374. A 24-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of GSK573719/GW642444 inhalation powder and the individual components delivered once-daily via a novel dry powder inhaler in subjects with chronic obstructive pulmonary disease. www.gsk-clinicalstudyregister.com/files2/gsk-113373-clinical-study-report-redact-v03.pdf (first received 30 March 2011).

Donohue 2015a ***{published and unpublished data}***
* Donohue JF, Worsley S, Zhu CQ, Hardaker L, Church A. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respiratory Medicine* 2015;**109**(7):870–81. PUBMED: 26006754]
GSK DB2114930. DB2114930: a randomized, multi-center, double-blind, double-dummy, parallel group study to evaluate the efficacy and safety of umeclidinium/vilanterol compared with fluticasone propionate/salmeterol over 12 weeks in subjects with COPD. www.gsk-clinicalstudyregister.com/files2/gsk-114930-clinical-study-report-redact.pdf (first received 26 March 2013).

Donohue 2015b ***{published and unpublished data}***
* Donohue JF, Worsley S, Zhu CQ, Hardaker L, Church A. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respiratory Medicine* 2015;**109**(7):870–81. PUBMED: 26006754]
GSK DB2114951. DB2114951: a randomized, multi-center, double-blind, double-dummy, parallel group study to evaluate the efficacy umeclidinium/vilanterol compared with fluticasone propionate/salmeterol over 12 weeks in subjects with COPD. www.gsk-clinicalstudyregister.com/files2/gsk-114951-protocol-redact.pdf (first received 29 July 2013).

Donohue 2016a ***{published and unpublished data}***
* Donohue JF, Soong W, Wu X, Shrestha P, Lei A. Long-term safety of aclidinium bromide/formoterol fumarate fixed-dose combination: results of a randomized 1-year trial in patients with COPD. *Respiratory Medicine* 2016;**116**:41–8. PUBMED: 27296819]
The Federal Joint Committee (G-BA) in Germany. Resolution by the Federal Joint Committee on an amendment to the Pharmaceutical Directive (AM-RL): Appendix XII - Resolutions on the benefit assessment of pharmaceuticals with new active ingredients, in accordance with the German Social Code, Book Five (SGB V), section 35a aclidinium bromide/formoterol. www.english.g-ba.de/downloads/91-1028-156/Aclidinium%20 bromide_formoterol_en.pdf (accessed prior to 15 August 2018).

Dransfield 2014 ***{published and unpublished data}***
* Dransfield MT, Feldman G, Korenblat P, LaForce CF, Locantore N, Pistolesi M, et al. Efficacy and safety of once-

daily fluticasone furoate/vilanterol (100/25 mcg) versus twice-daily fluticasone propionate/salmeterol (250/50 mcg) in COPD patients. *Respiratory Medicine* 2014;**108**(8): 1171–9. PUBMED: 24998880]
GSK HZC112352. A 12-week study to evaluate the 24-hour pulmonary function profile of fluticasone furoate/vilanterol (FF/VI) inhalation powder 100/25 mcg once daily compared with fluticasone propionate/salmeterol inhalation powder 250/50 mcg twice daily in subjects with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/gsk-112352-clinical-study-report-redact.pdf (first received 18 March 2011).
GSK HZC113109. A 12-week study to evaluate the 24-hour pulmonary function profile of fluticasone furoate/vilanterol (FF/VI) inhalation powder 100/25 mcg once daily compared with fluticasone propionate/salmeterol inhalation powder 250/50 mcg twice daily in subjects with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/gsk-113109-clinical-study-report-redact.pdf (first received 18 March 2011).
GSK RLV116974. A 12-week study to evaluate the 24-hour pulmonary function profile of fluticasone furoate/vilanterol (FF/VI) inhalation powder 100/25 mcg once daily compared with fluticasone propionate/salmeterol inhalation powder 250/50 mcg twice daily in subjects with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/gsk-116974-clinical-study-report-redact.pdf (first received 15 October 2012).

Feldman 2016 ***{published and unpublished data}***
* Feldman G, Maltais F, Khindri S, Vahdati-Bolouri M, Church A, Fahy WA, et al. A randomized, blinded study to evaluate the efficacy and safety of umeclidinium 62.5 μg compared with tiotropium 18 μg in patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease* 2016;**11**:719–30. PUBMED: 27103795]
GSK573719. A randomized, blinded, double-dummy, parallel-group study to evaluate the efficacy and safety of umeclidinium (UMEC) 62.5 mcg compared with tiotropium 18 mcg in subjects with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/gsk-201316-clinical-study-report-redact.pdf (first received 30 September 2014).

Ferguson 2008 ***{published and unpublished data}***
* Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. *Respiratory Medicine* 2008;**102**(8):1099–108. PUBMED: 18614347]
GSK SCO40043. A randomized, double-blind, parallel group, 52-week study to compare the effect of fluticasone propionate/salmeterol Diskus inhaler combination product 250/50mcg twice daily with salmeterol Diskus inhaler 50mcg twice daily on the annual rate of moderate/severe exacerbations in subjects with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/gsk-sco40043-clinical-study-report-redact.pdf (first received 26 October 2004).

Ferguson 2016 ***{published and unpublished data}***
Ferguson GT, Taylor AF, Thach C, Wang Q, Schubert-Tennigkeit AA, Patalano F, et al. Long-term maintenance bronchodilation with indacaterol/glycopyrrolate versus indacaterol in moderate-to-severe COPD patients: the FLIGHT 3 study. *International Journal of Chronic Obstructive Pulmonary Disease* 2016;**3**(4):716–28. PUBMED: 28848898]

Ferguson 2017 ***{published and unpublished data}***
Ferguson GT, Tashkin DP, Skärby T, Jorup C, Sandin K, Greenwood M, et al. Effect of budesonide/formoterol pressurized metered-dose inhaler on exacerbations versus formoterol in chronic obstructive pulmonary disease: the 6-month, randomized RISE (Revealing the Impact of Symbicort in reducing Exacerbations in COPD) study. *Respiratory Medicine* 2017;**132**:31–41. PUBMED: 29229103]
* NCT02157935. Comparing the efficacy of Symbicort pMDI and formoterol Turbuhaler in reducing exacerbations in patients with chronic obstructive pulmonary disease (RISE) [A phase IIIB, 6–month, double–blind, double–dummy, randomized, parallel–group, multicenter exacerbation study of Symbicort pressurized metered–dose inhaler (pMDI) 160/4.5 μg x 2 actuations twice–daily compared to formoterol Turbuhaler 4.5 μg x 2 inhalations twice–daily in chronic obstructive pulmonary disease (COPD) patients]. clinicaltrials.gov/ct2/show/NCT02157935 (first received 6 June 2014).

Fukuchi 2013 ***{published and unpublished data}***
* Fukuchi Y, Samoro R, Fassakhov R, Taniguchi H, Ekelund J, Carlsson LG, et al. Budesonide/formoterol via Turbuhaler versus formoterol via Turbuhaler in patients with moderate to severe chronic obstructive pulmonary disease: phase III multinational study results. *Respirology* 2013;**18**(5):866–73. PUBMED: 23551359]
NCT 01069289. Efficacy and safety study of Symbicort Turbuhaler versus Oxis Turbuhaler in chronic obstructive pulmonary disease (COPD) patients (SUMIRE) [A phase III, 12–week, double–blind, randomised, parallel–group, active controlled, multinational, efficacy and safety study of Symbicort Turbuhaler 160/4.5 μg 2 inhalations bid compared to Oxis Turbuhaler 4.5 μg 2 inhalations bid in patients with chronic obstructive pulmonary disease (COPD)]. clinicaltrials.gov/ct2/show/study/NCT01069289 (first received 17 February 2010).

GLOW4 2012 ***{published and unpublished data}***
NCT01119937. Long term safety and tolerability of NVA237 versus tiotropium in Japanese patients (GLOW4) [A 52–week treatment, multi–center, randomized, open label, parallel group study to assess the long term safety and tolerability of NVA237 (50µg o.d.) using tiotropium (18µg o.d.) as an active control in Japanese patients with moderate to severe chronic obstructive pulmonary disease]. clinicaltrials.gov/ct2/show/NCT01119937 (first received 10 May 2010).

Hagedorn 2013 ***{published and unpublished data}***
Hagedorn C, Kässner F, Banik N, Ntampakas P, Fielder K. Influence of salmeterol/fluticasone via single versus separate inhalers on exacerbations in severe/very severe COPD. *Respiratory Medicine* 2013;**107**(4):542–9. PUBMED: 23337300]

Hanania 2003 ***{published and unpublished data}***
GSK FCA3007. A randomized, double-blind, placebo-controlled, parallel-group, trial evaluating the safety and efficacy of the Diskus formulation of salmeterol 50mcg twice daily and fluticasone propionate 250mcg twice daily individually and in combination as compared to placebo in COPD patients. www.gsk-clinicalstudyregister.com/files2/sfca3007-clinical-study-report-redact-v02.pdf (first received 10 November 1998).
Hanania NA, Darken P, Horstman D, Reisner C, Lee B, Davis S, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. *Chest* 2003;**124**(3):834–43. PUBMED: 12970006]

Hanania 2017 ***{published and unpublished data}***
Hanania NA, Tashkin DP, Kerwin EM, Donohue JF, Denenberg M, O'Donnell DE, et al. Long-term safety and efficacy of glycopyrrolate/formoterol metered dose inhaler using novel Co-Suspension™ Delivery Technology in patients with chronic obstructive pulmonary disease. *Respiratory Medicine* 2017;**126**:105–15. PUBMED: 28427541]

Hoshino 2013 ***{published and unpublished data}***
Hoshino M, Ohtawa J. Effects of tiotropium and salmeterol/fluticasone propionate on airway wall thickness in chronic obstructive pulmonary disease. *Respiration* 2013;**86**(4):280–7. PUBMED: 23880883]

Hoshino 2014 ***{published and unpublished data}***
Hoshino M, Ohtawa J. Computed tomography assessment of airway dimensions with combined tiotropium and indacaterol therapy in COPD patients. *Respirology* 2014;**19**(3):403–10. PUBMED: 24708031]

Hoshino 2015 ***{published and unpublished data}***
Hoshino M, Ohtawa J, Akitsu K. Comparison of airway dimensions with once daily tiotropium plus indacaterol versus twice daily Advair in chronic obstructive pulmonary disease. *Pulmonary Pharmacology & Therapeutics* 2015;**30**:128–33. PUBMED: 25183687]

Jones 2011 ***{published and unpublished data}***
Jones PW, Mahler DA, Gale R, Owen R, Kramer B. Profiling the effects of indacaterol on dyspnoea and health status in patients with COPD. *Respiratory Medicine* 2011;**105**(6):892–9. PUBMED: 21397482]

Kalberg 2016 ***{published and unpublished data}***
GSK DB2116961. Study DB2116961, a multicentre, randomised, blinded, parallel group study to compare UMEC/VI (umeclidinium/vilanterol) in a fixed dose combination with indacaterol plus tiotropium in symptomatic subjects with moderate to very severe COPD. www.gsk-clinicalstudyregister.com/files2/gsk-116961-clinical-study-report-redact.pdf (first received 15 October 2014).
* Kalberg C, O'Dell D, Galkin D, Newlands A, Fahy WA. Dual bronchodilator therapy with umeclidinium/vilanterol versus tiotropium plus indacaterol in chronic obstructive pulmonary disease: a randomized controlled trial. *Drugs in R&D* 2016;**16**(2):217–27. PUBMED: 27028749]

Kardos 2007 ***{published and unpublished data}***
Kardos P, Wencker M, Glaab T, Vogelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2007;**175**(2):144–9. PUBMED: 17053207]

Kerwin 2012a ***{published and unpublished data}***
* Kerwin E, Hébert J, Gallagher N, Martin C, Overend T, Alagappan VK, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. *European Respiratory Journal* 2012;**40**(5):1106–14. PUBMED: 23060624]
NCT00929110. A 52-week treatment, randomized, double-blind, placebo-controlled, with open-label tiotropium, parallel-group study to assess the efficacy, safety, and tolerability of glycopyrronium bromide (NVA237) in patients with chronic obstructive pulmonary disease. clinicaltrials.gov/ct2/show/NCT00929110 (first received 26 June 2009).

Kerwin 2017 ***{published and unpublished data}***
GSK DB2116960. A randomized, double-dummy, parallel group, multicenter trial comparing the efficacy and safety of UMEC/VI (a fixed combination of umeclidinium and vilanterol) with tiotropium in subjects with COPD who continue to have symptoms on tiotropium. www.gsk-clinicalstudyregister.com/files2/gsk-116960-clinical-study-report-redact.pdf (first received 15 September 2014).
* Kerwin EM, Kalberg CJ, Galkin DV, Zhu CQ, Church A, Riley JH. Umeclidinium/vilanterol as step-up therapy from tiotropium in patients with moderate COPD: a randomized, parallel-group, 12-week study. *International Journal of Chronic Obstructive Pulmonary Disease* 2017;**12**:745–55. PUBMED: 28280319]

Koch 2014 ***{published and unpublished data}***
Koch A, Pizzichini E, Hamilton A, Hart L, Korducki L, De Salvo MC, et al. Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat versus placebo and formoterol twice daily in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. *International Journal of Chronic Obstructive Pulmonary Disease* 2014;**9**:697–714. PUBMED: 25045258]

Kornmann 2011 ***{published and unpublished data}***
Kornmann O, Dahl R, Centanni S, Dogra A, Owen R, Lassen C, et al. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. *European Respiratory Journal* 2011;**37**(2):273–9. PUBMED: 20693243]

Koser 2010 ***{published and unpublished data}***
GlaxoSmithKline. A randomized, double-blind, double-dummy, parallel group 12-week comparison of the efficacy and safety of fluticasone propionate/salmeterol hydrofluoroalkane 134a metered-dose-inhaler 230/42mcg twice-daily with fluticasone propionate/salmeterol diskus 250/50mcg twice-daily in subjects with copd. www.gsk-clinicalstudyregister.com/files2/adc111117-clinical-study-report-redact.pdf 2014.
* Koser A, Westerman J, Sharma S, Emmett A, Crater GD. Safety and efficacy of fluticasone propionate/salmeterol hydrofluoroalkane 134a metered-dose-inhaler compared with fluticasone propionate/salmeterol diskus in patients with chronic obstructive pulmonary disease. *Open Respiratory Medicine Journal* 2010;**4**:86–9. PUBMED: 21253451]

Mahler 2002 ***{published and unpublished data}***
GlaxoSmithKline. A randomized, double-blind, placebo-controlled, parallel-group, trial evaluating the safety and efficacy of the Diskus formulations of salmeterol 50mcg twice daily and fluticasone propionate 500mcg twice daily individually and in combination as compared to placebo in COPD patients. www.gsk-clinicalstudyregister.com/files2/gsk-sfca3006-clinical-study-report-redact-v02.pdf 2015.
* Mahler DA, Wire P, Horstman D, Chang CN, Yates J, Fischer T, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2002;**166**(8):1084–91. PUBMED: 12379552]

Mahler 2012a ***{published and unpublished data}***
* Mahler DA, D'Urzo A, Bateman ED, Ozkan SA, White T, Peckitt C, et al. Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison. *Thorax* 2012;**67**(9): 781–8. PUBMED: 22544891]
Novartis. A randomized, double-blind, controlled, parallel group, 12-week treatment study to compare the efficacy and safety of the combination of indacaterol 150 μg once daily with open label tiotropium 18 μg once daily versus open label tiotropium 18 μg once daily in patients with moderate-to severe chronic obstructive pulmonary disease. www.novctrd.com/CtrdWeb/displaypdf.nov?trialresultid= 3901 2011.

Mahler 2012b ***{published and unpublished data}***
* Mahler DA, D'Urzo A, Bateman ED, Ozkan SA, White T, Peckitt C, et al. Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison. *Thorax* 2012;**67**(9): 781–8. PUBMED: 22544891]
Novartis. A randomized, double-blind, controlled, parallel group, 12-week treatment study to compare the efficacy and safety of the combination of indacaterol 150 μg once daily with open label tiotropium 18 μg once daily versus open label tiotropium 18 μg once daily in patients with moderate-to severe chronic obstructive pulmonary disease. www.novctrd.com/CtrdWeb/displaypdf.nov?trialresultid= 3903 2011.

Mahler 2015a ***{published and unpublished data}***
Mahler DA, Kerwin E, Ayers T, FowlerTaylor A, Maitra S, Thach C, et al. FLIGHT1 and FLIGHT2: efficacy and safety of QVA149 (indacaterol/glycopyrrolate) versus its monocomponents and placebo in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2015;**192**(9): 1068–79. PUBMED: 26177074]

Mahler 2015b ***{published and unpublished data}***
Mahler DA, Kerwin E, Ayers T, FowlerTaylor A, Maitra S, Thach C, et al. FLIGHT1 and FLIGHT2: efficacy and safety of QVA149 (indacaterol/glycopyrrolate) versus its monocomponents and placebo in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2015;**192**(9): 1068–79.

Mahler 2016 ***{published and unpublished data}***
Mahler DA, Gifford AH, Satti A, Jessop N, Eckert JH, D'Andrea P, et al. Long-term safety of glycopyrrolate: a randomized study in patients with moderate-to-severe COPD (GEM3). *Respiratory Medicine* 2016;**115**:39–45. PUBMED: 27215502]

Maleki-Yazdi 2014 ***{published and unpublished data}***
GlaxoSmithKline. A multicenter, trial comparing the efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg once daily with tiotropium 18 mcg once daily over 24 weeks in subjects with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/gsk-117115-clinical-study-report-redact.pdf Dec 03, 2013.
* Maleki-Yazdi MR, Singh D, Anzueto A, Tombs L, Fahy WA, Naya I. Assessing short-term deterioration in maintenance-naïve patients with COPD receiving umeclidinium/vilanterol and tiotropium: a pooled analysis of three randomized trials. *Advances in Therapy* 2017;**33** (12):2188–99. PUBMED: 27796912]

Martinez 2017a ***{published and unpublished data}***
Martinez FJ, Rabe KF, Ferguson GT, Fabbri LM, Rennard S, Feldman GJ, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. *Chest* 2017;**151**(2):340–57. PUBMED: 27916620]

Martinez 2017b ***{published and unpublished data}***
Martinez FJ, Rabe KF, Ferguson GT, Fabbri LM, Rennard S, Feldman GJ, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. *Chest* 2017;**151**(2):340–57.

NCT00876694 2011 ***{unpublished data only}***
NCT00876694. A 52-week treatment, multi-center, randomized, open label, parallel group study to assess the long term safety and efficacy of indacaterol (300 µg o.d.) using salmeterol (50 µg b.i.d.) as an active control in Japanese patients with chronic obstructive

pulmonary disease (COPD). clinicaltrials.gov/ct2/show/NCT00876694 (first received 7 April 2009).

NCT01536262 2014 ***{unpublished data only}***
NCT01536262. Japan long-term safety for tiotropium plus olodaterol [A randomised, double–blind, parallel–group study to assess the safety and efficacy of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed–dose combination (2.5µg / 5µg, 5µg / 5µg) and olodaterol (5 µg) delivered by the RESPIMAT inhaler in Japanese patients with chronic obstructive pulmonary disease (COPD)]. clinicaltrials.gov/ct2/show/NCT01536262 (first received 22 February 2012).

Ohar 2014 ***{published and unpublished data}***
GSK ADC113874. A randomized, double-blind, parallel group, multicenter study of the effects of fluticasone propionate/salmeterol combination product 250/50mcg bid (Advair Diskus™) in comparison to salmeterol 50mcg bid (Serevent Diskus™) on the rate of exacerbations of COPD following hospitalization. www.gsk-clinicalstudyregister.com/files2/gsk-113874-clinical-study-report-redact.pdf (fist received 30 April 2010).
Ohar JA, Crater GD, Emmett A, Ferro TJ, Morris AN, Raphiou I, et al. Fluticasone propionate/salmeterol 250/50 μg versus salmeterol 50 μg after chronic obstructive pulmonary disease exacerbation. *Respiratory Research* 2014;**15**:105. PUBMED: 25248764]

Pepin 2014 ***{published and unpublished data}***
GSK HZC115247. A 12 week study to evaluate the effect of fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) 100/25 mcg inhalation powder delivered once daily via a novel dry powder inhaler (NDPI) on arterial stiffness compared with tiotropium bromide 18 mcg delivered once daily via a HandiHaler in subjects with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/gsk-115247-clinical-study-report-redact.pdf (first received 23 April 2012).
* Pepin JL, Cockcroft JR, Midwinter D, Sharma S, Rubin DB, Andreas S. Long-acting bronchodilators and arterial stiffness in patients with COPD: a comparison of fluticasone furoate/vilanterol with tiotropium. *Chest* 2014;**146**(6):1521–30. PUBMED: 25058845]

Perng 2009 ***{published and unpublished data}***
Perng DW, Tao CW, Su KC, Tsai CC, Liu LY, Lee YC. Anti-inflammatory effects of salmeterol/fluticasone, tiotropium/fluticasone or tiotropium in COPD. *European Respiratory Journal* 2009;**33**(4):778–84. PUBMED: 19129278]

RADIATE 2016 ***{unpublished data only}***
Larbig M, Taylor AF, Maitra S, Schubert-Tennigkeit A, Banerji D. Efficacy and safety of IND/GLY (indacaterol/glycopyrronium) versus placebo and tiotropium in symptomatic patients with moderate-to-severe COPD: the 52-week RADIATE study. *Respirology* 2015;**20 (suppl 3)**:A438.
* NCT01610037. Comparison of long-term safety of the combination product QVA149A against placebo and standard of care treatment in chronic obstructive pulmonary disease patients with moderate to severe airflow limitation [A placebo and active controlled study to assess the long–term safety of once daily QVA149 for 52 weeks in chronic obstructive pulmonary disease (COPD) patients with moderate to severe airflow limitation]. clinicaltrials.gov/ct2/show/NCT01610037 (first received 1 June 2012).

Rennard 2009 ***{published and unpublished data}***
Rennard SI, Tashkin DP, McElhattan J, Goldman M, Ramachandran S, Martin UJ, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs* 2009;**69**(5):549–65. PUBMED: 19368417]

Rheault 2016 ***{published and unpublished data}***
GSK 201315. A randomized, parallel-group, open-label study to evaluate the efficacy and safety of umeclidinium (UMEC) 62.5 mcg compared with glycopyrronium 44 mcg in subjects with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/gsk-201315-clinical-study-report-redact.pdf (first received 26 September 2014).
* Rheault T, Khindri S, Vahdati-Bolouri M, Church A, Fahy WA. A randomised, open-label study of umeclidinium versus glycopyrronium in patients with COPD. *ERJ Open Research* 2016;**2**(2):00101–2015. DOI: 10.1183/23120541.00101-2015; PUBMED: 27730198

Rossi 2014 ***{published and unpublished data}***
Rossi A, Van der Molen T, del Olmo R, Papi A, Wehbe L, Quinn M, et al. INSTEAD: a randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD. *European Respiratory Journal* 2014;**44**(6):1548–56. PUBMED: 25359348]

Sarac 2016 ***{published and unpublished data}***
Sarac P, Sayı ner A. Compare the efficacy and safety of long-acting anticholinergic and a combination of inhaled steroids and long-acting beta-2 agonist in moderate chronic obstructive pulmonary disease. *Tuberk Toraks* 2016;**64**(2):112–8. PUBMED: 27481077]

SCO100470 2006 ***{unpublished data only}***
GSK SCO100470. A multicentre, randomised, double-blind, parallel group, 24-week study to compare the effect of the salmeterol/fluticasone propionate combination product 50/250mcg, with salmeterol 50mcg both delivered twice daily via the Diskus/Accuhaler inhaler on lung function and dyspnoea in subjects with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/gsk-sco100470-clinical-study-report-redact-v02.pdf (first received 22 June 2004).

SCO40034 2005 ***{unpublished data only}***
GSK SCO40034. A multicentre, randomised, double-blind, double dummy, parallel group 12-week exploratory study to compare the effect of the salmeterol/fluticasone propionate combination product (Seretide™) 50/500mcg bd via the Diskus™/Accuhaler™ inhaler with tiotropium

bromide 18 mcg od via the HandiHaler inhalation device on efficacy and safety in patients with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/23678.pdf (first received 3 March 2003).

SCO40041 2008 ***{unpublished data only}***
GSK SCO40041. A randomized, double-blind, parallel-group clinical trial evaluating the effect of the fluticasone propionate/salmeterol combination product 250/50mcg twice daily via Diskus inhaler versus salmeterol 50mcg twice daily via Diskus inhaler on bone mineral density in subjects with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/gsk-sco40041-clinical-study-report-redact.pdf (first received 28 April 2004).

Sharafkhaneh 2012 ***{published and unpublished data}***
Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Martin UJ. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. *Respiratory Medicine* 2012;**106**(2):257–68. PUBMED: 22033040]

Singh 2014 ***{published and unpublished data}***
European Medicines Agency. Assessment report Duaklir Genuair. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003745/WC500178415.pdf (accessed prior to 29 August 2018).
* Singh D, Jones PW, Bateman ED, Korn S, Serra C, Molins E, et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. *BMC Pulmonary Medicine* 2014;**14**:178. PUBMED: 25404569]
The Federal Joint Committee (G-BA), Germany. Resolution by the Federal Joint Committee on an amendment to the Pharmaceutical Directive (AM-RL): Appendix XII - Resolutions on the benefit assessment of pharmaceuticals with new active ingredients, in accordance with the German Social Code, Book Five (SGB V), section 35a aclidinium bromide/formoterol. www.english.g-ba.de/downloads/91-1028-156/Aclidinium%20bromide_formoterol_en.pdf (accessed prior to 29 August 2018).

Singh 2015a ***{published and unpublished data}***
Singh D, Ferguson GT, Bolitschek J, Grönke L, Hallmann C, Bennett N, et al. Tiotropium + olodaterol shows clinically meaningful improvements in quality of life. *Respiratory Medicine* 2015;**109**(10):1312–9.

Singh 2015a&b ***{published and unpublished data}***
* Singh D, Ferguson GT, Bolitschek J, Grönke L, Hallmann C, Bennett N, et al. Tiotropium + olodaterol shows clinically meaningful improvements in quality of life. *Respiratory Medicine* 2015;**109**(10):1312–9. PUBMED: 26320402]

Singh 2015b ***{published and unpublished data}***
Singh D, Ferguson GT, Bolitschek J, Grönke L, Hallmann C, Bennett N, et al. Tiotropium + olodaterol shows clinically meaningful improvements in quality of life. *Respiratory Medicine* 2015;**109**(10):1312–9.

Singh 2015c ***{published and unpublished data}***
GSK DB2116134. DB2116134: a randomized, multi-center, double-blind, double-dummy, parallel group study to evaluate the efficacy and safety of umeclidinium bromide/vilanterol compared with fluticasone propionate/salmeterol over 12 weeks in subjects with COPD. www.gsk-clinicalstudyregister.com/files2/gsk-116134-clinical-study-report-redact.pdf (first received 2 April 2013).
* Singh D, Worsley S, Zhu CQ, Hardaker L, Church A. Umeclidinium/vilanterol versus fluticasone propionate/salmeterol in COPD: a randomised trial. *BMC Pulmonary Medicine* 2015;**15**:91. PUBMED: 26286141]

Szafranski 2003 ***{published and unpublished data}***
Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *European Respiratory Journal* 2003;**21**(1):74–81. PUBMED: 12570112]

Tashkin 2008 ***{published and unpublished data}***
Tashkin DP, Rennard SI, Martin P, Ramachandran S, Martin UJ, Silkoff PE, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. *Drugs* 2008;**68**(14):1975–2000. PUBMED: 18778120]

Tashkin 2009 ***{published and unpublished data}***
Tashkin DP, Pearle J, Lezzoni D, Varghese ST. Formoterol and tiotropium compared with tiotropium alone for treatment of COPD. *COPD* 2009;**6**(1):17–25. PUBMED: 19229704]

Tashkin 2012a ***{published and unpublished data}***
Tashkin DP, Doherty DE, Kerwin E, Matiz-Bueno CE, Knorr B, Shekar T, et al. Efficacy and safety characteristics of mometasone furoate/formoterol fumarate fixed-dose combination in subjects with moderate to very severe COPD: findings from pooled analysis of two randomized, 52-week placebo-controlled trials. *International Journal of Chronic Obstructive Pulmonary Disease* 2012;**7**:73–86.

Tashkin 2012a&b ***{published and unpublished data}***
Doherty DE, Tashkin DP, Kerwin E, Knorr BA, Shekar T, Banerjee S, et al. Effects of mometasone furoate/formoterol fumarate fixed-dose combination formulation on chronic obstructive pulmonary disease (COPD): results from a 52-week phase III trial in subjects with moderate-to-very severe COPD. *International Journal of Chronic Obstructive Pulmonary Disease* 2012;**7**:57–71. PUBMED: 22334769]
* Tashkin DP, Doherty DE, Kerwin E, Matiz-Bueno CE, Knorr B, Shekar T, et al. Efficacy and safety characteristics of mometasone furoate/formoterol fumarate fixed-dose combination in subjects with moderate to very severe

COPD: findings from pooled analysis of two randomized, 52-week placebo-controlled trials. *International Journal of Chronic Obstructive Pulmonary Disease* 2012;**7**:73–86. PUBMED: 22334770]

Tashkin 2012b ***{published and unpublished data}***
Tashkin DP, Doherty DE, Kerwin E, Matiz-Bueno CE, Knorr B, Shekar T, et al. Efficacy and safety characteristics of mometasone furoate/formoterol fumarate fixed-dose combination in subjects with moderate to very severe COPD: findings from pooled analysis of two randomized, 52-week placebo-controlled trials. *International Journal of Chronic Obstructive Pulmonary Disease* 2012;**7**:73–86.

To 2012 ***{published and unpublished data}***
To Y, Kinoshita M, Lee SH, Hang LW, Ichinose M, Fukuchi Y, et al. Assessing efficacy of indacaterol in moderate and severe COPD patients: a 12-week study in an Asian population. *Respiratory Medicine* 2012;**106**(12):1715–21. PUBMED: 23040786]

Troosters 2016 ***{published and unpublished data}***
Troosters T, Bourbeau J, Maltais F, Leidy N, Erzen D, De Sousa D, et al. Enhancing exercise tolerance and physical activity in COPD with combined pharmacological and non-pharmacological interventions: PHYSACTO randomised, placebo-controlled study design. *BMJ Open* 2016;**6**(4): e010106. PUBMED: 27075841]

Vincken 2014 ***{published and unpublished data}***
Vincken W, Aumann J, Chen H, Henley M, McBryan D, Goyal P. Efficacy and safety of coadministration of once-daily indacaterol and glycopyrronium versus indacaterol alone in COPD patients: the GLOW6 study. *International Journal of Chronic Obstructive Pulmonary Disease* 2014;**9**: 215–28. PUBMED: 24596459]

Vogelmeier 2008 ***{published and unpublished data}***
Vogelmeier C, Kardos P, Harari S, Gans SJ, Stenglein S, Thirlwell J. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. *Respiratory Medicine* 2008;**102**(11):1511–20. PUBMED: 18804362]

Vogelmeier 2011 ***{published and unpublished data}***
Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012, Issue 9. DOI: 10.1002/14651858.CD009157
* Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Mölken MP, Beeh KM, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *New England Journal of Medicine* 2011;**364**(12):1093–103. PUBMED: 21428765]

Vogelmeier 2013a ***{published and unpublished data}***
Vogelmeier CF, Bateman ED, Pallante J, Alagappan VK, D'Andrea P, Chen H, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respiratory Medicine* 2013;**1**(1):51–60. PUBMED: 24321804]

Vogelmeier 2016 ***{published and unpublished data}***
Vogelmeier C, Paggiaro PL, Dorca J, Sliwinski P, Mallet M, Kirsten AM, et al. Efficacy and safety of aclidinium/formoterol versus salmeterol/fluticasone: a phase 3 COPD study. *European Respiratory Journal* 2016;**48**(4):1030–39. PUBMED: 27492833]

Vogelmeier 2017 ***{published and unpublished data}***
NCT 01985334. Study to evaluate the efficacy and safety of glycopyrronium or indacaterol maleate and glycopyrronium bromide fixed-dose combination regarding symptoms and health status in patients with moderate COPD switching from treatment with any standard COPD regimen [A prospective, multicenter, 12–week, randomized open–label study to evaluate the efficacy and safety of glycopyrronium (50 micrograms o.d.) or indacaterol maleate and glycopyrronium bromide fixed–dose combination (110/50 micrograms o.d.) regarding symptoms and health status in patients with moderate chronic obstructive pulmonary disease (COPD) switching from treatment with any standard COPD regimen]. clinicaltrials.gov/ct2/show/NCT01985334 (first received 15 November 2013).
* Vogelmeier CF, Gaga M, Aalamian-Mattheis M, Greulich T, Marin JM5, Castellani W, et al. Efficacy and safety of direct switch to indacaterol/glycopyrronium in patients with moderate COPD: the CRYSTAL open-label randomised trial. *Respiratory Research* 2017;**18**(1):140. PUBMED: 28720132]

Wedzicha 2008 ***{published and unpublished data}***
GlaxoSmithKline SCO40036. Multicentre, randomised, double-blind, double dummy, parallel group, 104-week study to compare the effect of the salmeterol/fluticasone propionate combination product (Seretide*) 50/500mcg delivered twice daily via the Diskus*/Acchuhaler* inhaler with tiotropium bromide 18 mcg delivered once daily via the HandiHaler inhalation device on the rate of health care utilisation exacerbations in subjects with severe chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/gsk-sco40036-clinical-study-report-redact.pdf (first received 5 June 2003).
* Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *American Journal of Respiratory and Critical Care Medicine* 2008;**177**(1):19–26. PUBMED: 17916806]

Wedzicha 2013 ***{published and unpublished data}***
EudraCT 2009-013256-69. A 64-week treatment, multi-center, randomized, double-blind, parallel-group, active controlled study to evaluate the effect of QVA149 (110/50 μg o.d.) vs NVA237 (50 μg o.d.) and open-label tiotropium (18 μg o.d.) on COPD exacerbations in patients with severe to very severe chronic obstructive pulmonary disease (COPD). www.clinicaltrialsregister.eu/ctr-search/trial/2009-013256-69/AT#B (first received 28 April 2010).
* Wedzicha JA, Decramer M, Ficker JH, Niewoehner DE, Sandström T, Taylor AF, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual

bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respiratory Medicine* 2013;**1**(3): 199–209. PUBMED: 24429126]

Wedzicha 2014 ***{published and unpublished data}***
Wedzicha JA, Singh D, Vestbo J, Paggiaro PL, Jones PW, Bonnet-Gonod F, et al. Extrafine beclomethasone/ formoterol in severe COPD patients with history of exacerbations. *Respiratory Medicine* 2014;**108**(8):1153–62. PUBMED: 24953015]

Wedzicha 2016 ***{published and unpublished data}***
Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *New England Journal of Medicine* 2016;**374**(23):2222–34. PUBMED: 27181606]

Wise 2013 ***{published and unpublished data}***
Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B, et al. Tiotropium Respimat inhaler and the risk of death in COPD. *New Egyptian Journal of Medicine* 2013;**369**(16): 1491–501. PUBMED: 23992515]

Yao 2014 ***{published and unpublished data}***
Yao W, Wang C, Zhong N, Han X, Wu C, Yan X, et al. Effect of once-daily indacaterol in a predominantly Chinese population with chronic obstructive pulmonary disease: a 26-week Asia-Pacific study. *Respirology* 2014;**19**(2):231–8. PUBMED: 24383720]

Zhong 2015 ***{published and unpublished data}***
Zhong N, Wang C, Zhou X, Zhang N, Humphries M, Wang L, et al. LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease* 2015;**10**:1015–26. PUBMED: 26082625]

ZuWallack 2014a ***{published and unpublished data}***
ZuWallack R, Allen L, Hernandez G, Ting N, Abrahams R. Efficacy and safety of combining olodaterol Respimat and tiotropium HandiHaler in patients with COPD: results of two randomized, double-blind, active-controlled studies. *International Journal of Chronic Obstructive Pulmonary Disease* 2014;**9**:1133–44.

ZuWallack 2014a&b ***{published and unpublished data}***
ZuWallack R, Allen L, Hernandez G, Ting N, Abrahams R. Efficacy and safety of combining olodaterol Respimat and tiotropium HandiHaler in patients with COPD: results of two randomized, double-blind, active-controlled studies. *International Journal of Chronic Obstructive Pulmonary Disease* 2014;**9**:1133–44. PUBMED: 25342898]

ZuWallack 2014b ***{published and unpublished data}***
ZuWallack R, Allen L, Hernandez G, Ting N, Abrahams R. Efficacy and safety of combining olodaterol Respimat and tiotropium HandiHaler in patients with COPD: results of two randomized, double-blind, active-controlled studies. *International Journal of Chronic Obstructive Pulmonary Disease* 2014;**9**:1133–44.

References to studies excluded from this review

1237.20 ***{unpublished data only}***
NCT01559116. Characterization of 24-hour lung function profiles of inhaled tiotropium + olodaterol fixed dose combination in patients suffering from chronic obstructive pulmonary disease [Randomised, double–blind, placebo–controlled, 6 treatment, 4 period, incomplete cross–over trial to characterise the 24–hour lung function profiles of tiotropium + olodaterol fixed dose combination (2.5/5 µg, 5/5 µg), tiotropium (2.5 µg, 5 µg) and olodaterol (5 µg) (oral inhalation, delivered by the Respimat Inhaler) after 6 weeks once daily treatment in patients with chronic obstructive pulmonary disease (COPD) [VIVACITOTM]]. clinicaltrials.gov/ct2/show/NCT01559116 (first received 21 March 2012). NCT01559116]

1237.4 ***{unpublished data only}***
NCT00696020. Combination of orally inhaled bi1744cl/ tiotropium bromide in patients with chronic obstructive pulmonary disease (COPD). Randomised, double-blind, parallel group study to assess the efficacy and safety of 4 weeks of once daily treatment of 3 doses of orally inhaled bi 1744 cl, each in fixed dose combination with 5 microgram tiotropium bromide (delivered by the Respimat inhaler) compared with 5 microgram tiotropium bromide monoproduct (delivered by the Respimat inhaler) in patients with COPD. clinicaltrials.gov/ct2/show/NCT00696020 (first received June 12, 2008). NCT00696020]

1237.7 ***{unpublished data only}***
Boehringer Ingelheim. A randomised, placebo-controlled, double-blind, single dose, cross-over study to evaluate the efficacy and safety of orally inhaled tiotropium + olodaterol as both a fixed dose combination and a free combination (both delivered by the Respimat inhaler) in patients with chronic obstructive pulmonary disease (COPD). clinicaltrials.gov/ct2/show/NCT02030535 (first received January 8, 2014). NCT02030535]

Bateman 2010 ***{published data only}***
Bateman E, Singh D, Smith D, Disse B, Towse L, Massey D, et al. Efficacy and safety of tiotropium Respimat SMI in COPD in two 1-year randomized studies. *International Journal of Chronic Obstructive Pulmonary Disease* 2010;**5**: 197–208. PUBMED: 20714373]

Beeh 2014 ***{published data only}***
Beeh KM, Korn S, Beier J, Jadayel D, Henley M, D'Andrea P, et al. Effect of QVA149 on lung volumes and exercise tolerance in COPD patients: the BRIGHT study. *Respiratory Medicine* 2014 Apr;**108**(4):584–92. PUBMED: 24534204]

Beeh 2016 ***{published data only}***
Beeh KM, Derom E, Echave-Sustaeta J, Grönke L, Hamilton A, Zhai D, et al. The lung function profile of once-daily tiotropium and olodaterol via Respimat is superior to that of twice-daily salmeterol and fluticasone propionate via Accuhaler (ENERGITO study). *International Journal of Chronic Obstructive Pulmonary Disease* 2016;**11**:193–205. PUBMED: 26893551]

Berton 2016 ***{published data only}***
Berton DC, Santos ÁH, Bohn I Jr, Lima RQ, Breda V, Teixeira PJ. Effects of indacaterol versus tiotropium on exercise tolerance in patients with moderate COPD: a pilot randomized crossover study. *Jornal Brasileiro de Pneumologia* 2016;**42**(5):367–73. PUBMED: 27812637]

Celli 2014 ***{published data only}***
Celli B, Crater G, Kilbride S, Mehta R, Tabberer M, Kalberg CJ, et al. Once-daily umeclidinium/vilanterol 125/25 mcg in COPD: a randomized, controlled study. *Chest* 2014;**145**(5):981–91. PUBMED: 24385182]

CQAB149BIL01 ***{unpublished data only}***
Novartis Pharmaceuticals. A 12 week, multi-center, randomized, open label study, evaluating the efficacy and safety of treatment regimens that include Onbrez (indacaterol) in patients with moderate to severe COPD (MOVE-ON Study). clinicaltrials.gov/ct2/show/NCT01232894 (first received November 2, 2010).

CQMF149F2202 ***{unpublished data only}***
Novartis Pharmaceuticals. A randomized, double-blind, 12-week treatment, parallel-group study to evaluate the efficacy and safety of QMF149 (150 µg/160 µg o.d.) compared with salmeterol xinafoate/fluticasone propionate (50 µg/500 µg b.i.d.) in patients with chronic obstructive pulmonary disease. clinicaltrials.gov/ct2/show/NCT01636076 (first received July 10, 2012).

D'Urzo 2013 ***{published data only}***
D'Urzo A, Kerwin E, Rennard S, He T, Gil EG, Caracta C. One-year extension study of ACCORD COPD I: safety and efficacy of two doses of twice-daily aclidinium bromide in patients with COPD. *COPD* 2013;**10**(4):500–10. PUBMED: 23679347]

Dahl 2013 ***{published data only}***
Dahl R, Jadayel D, Alagappan VK, Chen H, Banerji D. Efficacy and safety of QVA149 compared to the concurrent administration of its monocomponents indacaterol and glycopyrronium: the BEACON study. *International Journal of Chronic Obstructive Pulmonary Disease* 2013;**8**:501–8. PUBMED: 24159259]

Donohue 2014 ***{published data only}***
Donohue JF, Niewoehner D, Brooks J, O'Dell D, Church A. Safety and tolerability of once-daily umeclidinium/vilanterol 125/25 mcg and umeclidinium 125 mcg in patients with chronic obstructive pulmonary disease: results from a 52-week, randomized, double-blind, placebo-controlled study. *Respiratory Research* 2014 Jul 11;**15**:78. PUBMED: 25015176]

Donohue 2016b ***{published and unpublished data}***
Donohue JF, Singh D, Munzu C, Kilbride S, Church A. Magnitude of umeclidinium/vilanterol lung function effect depends on monotherapy responses: results from two randomised controlled trials. *Respiratory Medicine* 2016;**112**:65–74. PUBMED: 26797016]

Dransfield 2013 ***{published and unpublished data}***
Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, Vestbo J, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respiratory Medicine* 2013;**1**(3):210–23. PUBMED: 24429127]

Fang 2008 ***{published and unpublished data}***
Fang LZ, Liang X, Zhang JQ, Liu L, Fu WP, Zhao ZH, et al. Combination of inhaled salmeterol/fluticasone and tiotropium in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Zhonghua Jie He He Hu Xi Za Zhi* 2008;**31**(11):811–4. PUBMED: 19080533]

Ferguson 2014 ***{published data only}***
Ferguson GT, Feldman GJ, Hofbauer P, Hamilton A, Allen L, Korducki L, et al. Efficacy and safety of olodaterol once daily delivered via Respimat in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. *International Journal of Chronic Obstructive Pulmonary Disease* 2014;**9**:629–45. PUBMED: 24966672]

Gelb 2013 ***{published data only}***
Gelb AF, Tashkin DP, Make BJ, Zhong X, Garcia Gil E, Caracta C, et al. Long-term safety and efficacy of twice-daily aclidinium bromide in patients with COPD. *Respiratory Medicine* 2013;**107**(12):1957–65. PUBMED: 23916502]

HZC113108 ***{unpublished data only}***
GlaxoSmithKline. A 24-week study to evaluate the effect of fluticasone furoate/vilanterol 100/25 mcg inhalation powder delivered once-daily via a novel dry powder inhaler on arterial stiffness compared with placebo and vilanterol in subjects with chronic obstructive pulmonary disease (COPD). clinicaltrials.gov/ct2/show/NCT01336608 (first received April 18, 2011).

Jones 1997 ***{published data only}***
Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. *American Journal of Respiratory and Critical Care Medicine* 1997;**155**(4):1283–9. PUBMED: 9105068]

Jones 2012 ***{published data only}***
Jones PW, Leidy NK, Hareendran A, Lamarca R, Chuecos F, Garcia Gil E. The effect of aclidinium bromide on daily respiratory symptoms of COPD, measured using the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) diary: pooled analysis of two 6-month phase III studies. *Respiratory Research* 2016;**17**(1):61. PUBMED: 27215749]

Kerwin 2012b ***{published data only}***
Kerwin EM, D'Urzo AD, Gelb AF, Lakkis H, Garcia Gil E, Caracta CF. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). *COPD* 2012;**9**(2):90–101. PUBMED: 22320148]

Kerwin 2013 ***{published and unpublished data}***
Kerwin EM, Scott-Wilson C, Sanford L, Rennard S, Agusti A, Barnes N, et al. A randomised trial of fluticasone furoate/vilanterol (50/25 μg; 100/25 μg) on lung function

in COPD. *Respiratory Medicine* 2013;**107**(4):560–9. PUBMED: 23352226]

Kurashima 2009 ***{published data only}***
Kurashima K, Hara K, Yoneda K, Kanauchi T, Kagiyama N, Tokunaga D, et al. Changes in lung function and health status in patients with COPD treated with tiotropium or salmeterol plus fluticasone. *Respirology* 2009;**14**(2):239–44. PUBMED: 19210650]

Lipson 2018 ***{published and unpublished data}***
* Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *New England Journal of Medicine* 2018;**378**(18):1671–80. PUBMED: 29668352]
Pascoe SJ, Lipson DA, Locantore N, Barnacle H, Brealey N, Mohindra R, et al. A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol. *European Respiratory Journal* 2016;**48**(2):320–30. PUBMED: 27418551]

Magnussen 2012 ***{published data only}***
Magnussen H, Paggiaro P, Schmidt H, Kesten S, Metzdorf N, Maltais F. Effect of combination treatment on lung volumes and exercise endurance time in COPD. *Respiratory Medicine* 2012;**106**(10):1413–20. PUBMED: 22749044]

Mahler 2014 ***{published data only}***
Mahler DA, Decramer M, D'Urzo A, Worth H, White T, Alagappan VK, et al. Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study. *European Respiratory Journal* 2014;**43**(6):1599–609. PUBMED: 24176997]

Mahmud 2007 ***{published data only}***
Mahmud AM, Gupta DK, Khan AS, Hassan R, Hossain A, Rahman M, et al. Comparison of once daily tiotropium with twice daily salmeterol in Bangladeshi patients with moderate COPD. Respirology. 2007:12 (Supple 4) A211.

Make 2014 ***{published data only}***
Make BJ, Donohue JF, Soong W, Zhong X, Leselbaum, A, Caracta C. Lung function and safety of aclidinium bromide/formoterol fumarate fixed-dose combination: results of a 1-year trial in patients with COPD. American Journal of Respiratory and Critical Care Medicine. 2014; Vol. 189: A6010.

Maltais 2014a ***{published data only}***
GlaxoSmithKline. An Exercise Endurance Study to Evaluate the Effects of Treatment of Chronic Obstructive Pulmonary Disease (COPD) Patients With a Dual Bronchodilator: GSK573719/GW642444. Study A (COPD). clinicaltrials.gov/ct2/show/NCT01328444 (first received April 4, 2011).

Maltais 2014b ***{published data only}***
GlaxoSmithKline. An exercise endurance study to evaluate the effects of treatment of chronic obstructive pulmonary disease (COPD) patients with a dual bronchodilator: GSK573719/GW642444.Study B (COPD). https://clinicaltrials.gov/ct2/show/NCT01323660 (first received March 25, 2011).

Maltais 2018 ***{published data only}***
Maltais F, O'Donnell D, Gáldiz Iturri JB, Kirsten AM, Singh D, Hamilton A, et al. Effect of 12 weeks of once-daily tiotropium/olodaterol on exercise endurance during constant work-rate cycling and endurance shuttle walking in chronic obstructive pulmonary disease. *Therapeutic Advances in Respiratory Disease* 2018;**12**: 1753465818755091. PUBMED: 29439648]

Martinez 2013 ***{published and unpublished data}***
* Martinez FJ, Boscia J, Feldman G, Scott-Wilson C, Kilbride S, Fabbri L, et al. Fluticasone furoate/vilanterol (100/25; 200/25 μg) improves lung function in COPD: a randomised trial. *Respiratory Medicine* 2013;**107**(4):550–9. PUBMED: 23332861]

MORACTO1 ***{unpublished data only}***
Boehringer Ingelheim. A randomised, double-blind, 5 treatment arms, 4-period, incomplete cross-over study to determine the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (FDC) (2.5 / 5 µg; and 5 / 5 µg) (delivered by the Respimat inhaler) compared with tiotropium (5 µg), olodaterol (5 µg) and placebo (delivered by the Respimat inhaler) on lung hyperinflation and exercise endurance time during constant work rate cycle ergometry in patients with chronic obstructive pulmonary disease (COPD) [MORACTO TM 1]. clinicaltrials.gov/ct2/show/NCT01533922 (first received February 16, 2012).

MORACTO2 ***{unpublished data only}***
Boehringer Ingelheim. A randomised, double-blind, 5 treatment arms, 4-period, incomplete cross-over study to determine the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (FDC) (2.5 / 5 µg; and 5 / 5 µg) (delivered by the Respimat inhaler) compared with tiotropium (5 µg), olodaterol (5 µg) and placebo (delivered by the Respimat inhaler) on lung hyperinflation and exercise endurance time during constant work rate cycle ergometry in patients with chronic obstructive pulmonary disease (COPD) [MORACTO TM 2]. clinicaltrials.gov/ct2/show/NCT01533935 (first received February 16, 2012).

PT003016-00 ***{unpublished data only}***
Pearl Therapeutics. An open-label, multi-center, dose indicator study of glycopyrronium and formoterol fumarate (GFF) metered dose inhaler (MDI) in adult subjects with moderate to very severe chronic obstructive pulmonary disease (COPD). clinicaltrials.gov/ct2/show/NCT02268396 (first received October 20, 2014).

Rabe 2008 ***{published data only}***
Rabe KF, Timmer W, Sagkriotis A, Viel K. Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. *Chest* 2008;**134**(2): 255–62. PUBMED: 18403672]

Rennard 2013 ***{published data only}***
Rennard SI, Scanlon PD, Ferguson GT, Rekeda L, Maurer BT, Garcia Gil E, et al. ACCORD COPD II: a randomized clinical trial to evaluate the 12-week efficacy and safety

of twice-daily aclidinium bromide in chronic obstructive pulmonary disease patients. *Clinical Drug Investigation* 2013;**33**(12):893–904. PUBMED: 24085591]

Rossi 2012 ***{published data only}***
Rossi A, Centanni S, Cerveri I, Gulotta C, Foresi A, Cazzola M, et al. Acute effects of indacaterol on lung hyperinflation in moderate COPD: a comparison with tiotropium. *Respiratory Medicine* 2012;**106**(1):84–90. PUBMED: 22035851]

SCO100646 ***{unpublished data only}***
GlaxoSmithKline. Clinical evaluation Of GW815SF for chronic obstructive pulmonary disease (chronic bronchitis, emphysema). clinicaltrials.gov/ct2/show/NCT00269126 (first received December 23, 2005).

Siler 2017 ***{published and unpublished data}***
Siler TM, Nagai A, Scott-Wilson CA, Midwinter DA, Crim C. A randomised, phase III trial of once-daily fluticasone furoate/vilanterol 100/25 μg versus once-daily vilanterol 25 μg to evaluate the contribution on lung function of fluticasone furoate in the combination in patients with COPD. *Respiratory Medicine* 2017;**123**:8–17. PUBMED: 28137501]

Singh 2016 ***{published data only}***
Singh D, Schröder-Babo W, Cohuet G, Muraro A, Bonnet-Gonod F, Petruzzelli S, et al. The bronchodilator effects of extrafine glycopyrronium added to combination treatment with beclometasone dipropionate plus formoterol in COPD: a randomised crossover study (the TRIDENT study). *Respiratory Medicine* 2016;**114**:84–90. PUBMED: 27109816]

Tashkin 2016 ***{published data only}***
Tashkin DP, Martinez FJ, Rodriguez-Roisin R, Fogarty C, Gotfried M, Denenberg M, et al. A multicenter, randomized, double-blind dose-ranging study of glycopyrrolate/formoterol fumarate fixed-dose combination metered dose inhaler compared to the monocomponents and open-label tiotropium dry powder inhaler in patients with moderate-to-severe COPD. *Respiratory Medicine* 2016;**120**:16–24. PUBMED: 27817811]

To 2011 ***{published data only}***
To Y, Nishimura M, Fukuchi Y, Kitawaki T, Okino N, et al. Long-term safety and tolerability of indacaterol versus salmeterol in Japanese COPD patients: a 52-week open-labeled study. Respirology. Conference: 16th Congress of the Asian Pacific Society of Respirology. 2011:16:96.

Van Noord 2010 ***{published data only}***
Van Noord JA, Aumann JL, Janssens E, Smeets JJ, Zaagsma J, Mueller A, et al. Combining tiotropium and salmeterol in COPD: effects on airflow obstruction and symptoms. *Respiratory Medicine* 2010;**104**(7):995–1004. PUBMED: 20303247]

Vestbo 2016 ***{published and unpublished data}***
Vestbo J, Anderson JA, Brook RD, Calverley PM, Celli BR, Crim C, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016;**30**:387. PUBMED: 27203508]

Vogelmeier 2010a ***{published data only}***
Vogelmeier C, Verkindre C, Cheung D, Galdiz JB, Güçlü SZ, Spangenthal S, et al. Safety and tolerability of NVA237, a once-daily long-acting muscarinic antagonist, in COPD patients. *Pulmonary Pharmacology & Therapeutics* 2010;**23**(5):438–44. PUBMED: 28737971]

Vogelmeier 2010b ***{published data only}***
Vogelmeier C, Ramos-Barbon D, Jack D, Piggott S, Owen R, Higgins M, et al. Indacaterol provides 24-hour bronchodilation in COPD: a placebo-controlled blinded comparison with tiotropium. *Respiration Physiology* 2010; **11**(1):135. PMC2964613]

Vogelmeier 2013b ***{published data only}***
Vogelmeier C, Fabbri LM, Rabe KF, Beeh KM, Schmidt H, Metzdorf N, et al. Effect of tiotropium vs. salmeterol on exacerbations: GOLD II and maintenance therapy naïve patients. *Respiratory Medicine* 2013;**107**(1):75–83. PUBMED: 23102611]

Watz 2016 ***{published data only}***
Watz H, Mailänder C, Baier M, Kirsten A. Effects of indacaterol/glycopyrronium (QVA149) on lung hyperinflation and physical activity in patients with moderate to severe COPD: a randomised, placebo-controlled, crossover study (The MOVE Study). *BMC Pulmonary Medicine* 2016;**16**(1):95. PUBMED: 27301417]

Wouters 2005 ***{published data only}***
Wouters EF, Postma DS, Fokkens B, Hop WC, Prins J, Kuipers AF, et al. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. *Thorax* 2005; **60**(6):480–7. PUBMED: 15923248]

Zheng 2015 ***{published data only}***
Zheng J, Zhong N, Newlands A, Church A, Goh AH. Efficacy and safety of once-daily inhaled umeclidinium/vilanterol in Asian patients with COPD: results from a randomized, placebo-controlled study. *International Journal of Chronic Obstructive Pulmonary Disease* 2015;**10**:1753–67. PMC4562726]

References to studies awaiting assessment

Calverley 2018 ***{published data only}***
Calverley PM, Anzueto AR, Carter K, Grönke L, Hallmann C, Jenkins C, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. *Lancet Respiratory Medicine* 2018 May;**6**(5):337–44.

Papi 2017 ***{published and unpublished data}***
Papi A, Dokic D, Tzimas W, Mészáros I, Olech-Cudzik A, Koroknai Z, et al. Fluticasone propionate/formoterol for COPD management: a randomized controlled trial. *International Journal of Chronic Obstructive Pulmonary Disease* 2017;**12**:1961–71. PUBMED: 28740376]

References to ongoing studies

AMPLIFY ***{unpublished data only}***

AstraZeneca. A 24 week treatment, multicenter, randomized, double blinded, double dummy, parallel-group, clinical trial evaluating the efficacy and safety of aclidinium bromide 400 μg/formoterol fumarate 12 μg fixed-dose combination bid compared with each monotherapy (aclidinium bromide 400 μg bid and formoterol fumarate 12 μg bid) and tiotropium 18 μg qd when administered to patients with stable chronic obstructive pulmonary disease. clinicaltrials.gov/ct2/show/NCT02796677 (first received June 13, 2016).

* Sethi S, Kerwin EM, Watz H, Ferguson GT, Mroz R, Segarra R, et al. AMPLIFY: A randomized, phase III study evaluating the efficacy and safety of aclidinium/formoterol versus monotherapy in patients with COPD. American Journal of Respiratory and Critical Care Medicine. 2018; Vol. 197:A4241.

AVANT ***{unpublished data only}***

* AstraZeneca. A 24-week treatment, randomised, parallel-group, double blinded, double-dummy, multicenter study to assess the efficacy and safety of aclidinium bromide/formoterol fumarate compared with individual components and placebo and aclidinium bromide compared with placebo when administered to patients with stable chronic obstructive pulmonary disease. clinicaltrials.gov/ct2/show/NCT03022097 (first received January 16, 2017).

FLASH ***{unpublished data only}***

* Frith P, Ashmawi S, Krishnamurthy S, Diaz D, Gurgun A, Hours-Zesiger P, et al. Assessing direct switch to indacaterol/glycopyrronium from salmeterol/fluticasone in moderate to severe symptomatic COPD patients: the FLASH Study. Respirology. 2017:AOL011.

Novartis Pharmaceuticals. Assessment of switching from salmeterol/fluticasone to indacaterol/glycopyrronium in a symptomatic COPD patient cohort (FLASH). clinicaltrials.gov/ct2/show/NCT02516592 (first received August 6, 2015). PUBMED: NCT02516592]

FLT3510 ***{unpublished data only}***

* Mundipharma Research. A randomised double-blind, double-dummy parallel group study to compare the efficacy and safety of fluticasone propionate / formoterol fumarate (Flutiform) 500/20 µg bid and 250/10 µg bid versus salmeterol / fluticasone (Seretide) 50/500 µg bid in subjects with chronic obstructive pulmonary disease (COPD). clinicaltrials.gov/ct2/show/NCT02195375 (first received July 21, 2014).

PINNACLE 4 ***{unpublished data only}***

* Pearl Therapeutics. A randomized, double-blind, chronic dosing (24 weeks), placebo-controlled, parallel group, multi-center study to assess the efficacy and safety of PT003, PT005, and PT001 in subjects with moderate to very severe COPD, compared with placebo. clinicaltrials.gov/ct2/show/NCT02343458 (first received January 22, 2015).

PT010006 ***{unpublished data only}***

* Pearl Therapeutics. A randomized, double-blind, parallel-group, 24-week, chronic-dosing, multi-center study to assess the efficacy and safety of PT010, PT003, and PT009 compared with Symbicort Turbuhaler as an active control in subjects with moderate to very severe chronic obstructive pulmonary disease. clinicaltrials.gov/ct2/show/NCT02497001 (first received July 14, 2015).

Additional references

ATS/ERS 2004

Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *European Respiratory Journal* 2004;**23**(6):932–46.

Chen 2017

Chen WC, Huang CH, Sheu CC, Chong IW, Chu KA8, Chen YC, et al. Long-acting beta2-agonists versus long-acting muscarinic antagonists in patients with stable COPD: a systematic review and meta-analysis of randomized controlled trials. *Respirology* 2017;**7**:1313–19. [PUBMED: 28654201]

Dechartres 2013

Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ* 2013;**346**:f2304.

Decramer 2012

Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *Lancet* 2012;**379**:1341–51.

Dias 2013a

Dias S, Welton NJ, Marinho VCC Salanti G, Higgins JP, Ades AE. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Medical Decision Making* 2013;**33**:607–17.

Dias 2013b

Dias S Welton NJ Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Medical Decision Making* 2013;**33**:641–56. [PUBMED: 23804508]

Dias 2013c

Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. *Medical Decision Making* 2013;**33**(5):618–40. [PUBMED: 23804507]

Dias 2018

Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. *Network Meta-Analysis for Decision-Making*. John Wiley & Sons, 2018. [ISBN 1118951727, 9781118951729]

Donohue 2015

Donohue JF, Worsley S, Zhu CQ, Hardaker L, Church A. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respiratory Medicine* 2015;**109**(7):870–81.

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**(7109):629–34.

Falk 2008
Falk JA, Minai OA, Mosenifar Z. Inhaled and systemic corticosteroids in chronic obstructive pulmonary disease. *Proceedings of the American Thoracic Society* 2008;**5**(4):506–12.

Farne 2015
Farne HA, Cates CJ. Long-acting beta2-agonist in addition to tiotropium versus either tiotropium or long-acting beta2-agonist alone for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2015, Issue 10. DOI: 10.1002/14651858.CD008989.pub3

GOLD 2018
2018 Global strategy for prevention, diagnosis and management of COPD. goldcopd.org/gold-reports/ (accessed 31 August 2018).

GRADEpro GDT 2015 [Computer program]
McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 7 July 2016. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Guyatt 2011a
Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence - imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283–93.

Guyatt 2011b
Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *Journal of Clinical Epidemiology* 2011;**64**(4):380–2.

Heidari 2012
Heidari B. The importance of C-reactive protein and other inflammatory markers in patients with chronic obstructive pulmonary disease. *Caspian Journal of Internal Medicine* 2012;**3**(2):428–35.

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

Higgins 2017
Higgins JP, Altman DG, Sterne JA (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Horita 2017
Horita N, Goto A, Shibata Y, Ota E, Nakashima K, Nagai K, et al. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). *Cochrane Database of Systematic Reviews* 2017, Issue 2. DOI: 10.1002/14651858.CD012066.pub2

Huisman 2015
Huisman EL, Cockle SM, Ismaila AS, Karabis A, Punekar YS. Comparative efficacy of combination bronchodilator therapies in COPD: a network meta-analysis. *International Journal of Chronic Obstructive Pulmonary Disease* 2015;**10**:1863–81.

Kew 2014
Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2014, Issue 3. DOI: 10.1002/14651858.CD010844.pub2

Kume 2014
Kume H, Imbe S, Nishiyama O, Iwanaga T, Higashimoto Y, Tohda Y. Involvement of regulation of KCa channels via Gi, Gs in the synergistic action between anticholinergic agents and β2-adrenergic receptor agonists in airway smooth muscle. *American Journal of Respiratory and Critical Care Medicine* 2014;**189**:A5589.

Mathieu 2009
Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. *JAMA* 2009;**302**(9):977–84.

McCarthy 2015
McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2015, Issue 2. DOI: 10.1002/14651858.CD003793.pub3

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000097. DOI: 10.1371/journal.pmed.1000097

Nannini 2012
Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012, Issue 9. DOI: 10.1002/14651858.CD006829.pub2

Nüesch 2010
Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ* 2010;**341**:c3515.

Oba 2016a
Oba Y, Sarva ST, Dias S. Efficacy and safety of long-acting beta-agonist/long-acting muscarinic antagonist combinations in COPD: a network meta-analysis. *Thorax* 2016;**71**(1):15–25.

Oba 2016b
Oba Y, Chandran A, Devasahayam J. Long-acting muscarinic antagonist versus inhaled corticosteroid when

added to long-acting β-agonist for COPD: a meta-analysis. *COPD* 2016;**13**(6):677–85.

Patel 2014
Patel JG, Nagar SP, Dalal AA. Indirect costs in chronic obstructive pulmonary disease: a review of the economic burden on employers and individuals in the United States. *International Journal of Chronic Obstructive Pulmonary Disease* 2014;**9**:289–300.

Review Manager 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rochester 2015
Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, et al. ATS/ERS Task Force on Policy in Pulmonary Rehabilitation. An official American Thoracic Society/European Respiratory Society policy statement. Enhancing implementation, use, and delivery of pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine* 2015;**192**(11):1373–86.

Rodrigo 2017
Rodrigo GJ, Price D, Anzueto A, Singh D, Altman P, Bader G, et al. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. *International Journal of Chronic Obstructive Pulmonary Disease* 2017;**12**:907–22. [PUBMED: 28360514]

Schlueter 2016
Schlueter M, Gonzalez-Rojas N, Baldwin M, Groenke L, Voss F, Reason T. Comparative efficacy of fixed-dose combinations of long-acting muscarinic antagonists and long-acting β2-agonists: a systematic review and network meta-analysis. *Therapeutic Advances in Respiratory Disease* 2016;**10**(2):89–104.

Singh 2015d
Singh D, Worsley S, Zhu CQ, Hardaker L, Church A. Umeclidinium/vilanterol versus fluticasone propionate/salmeterol in COPD: a randomised trial. *BMC Pulmonary Medicine* 2015;**15**:91.

Spiegelhalter 2002
Spiegelhalter DJ, Best NG, Carlin BP, Van der Linde A. Bayesian measures of model complexity and fit. *Journal of the Royal Statistical Society. Series B (Statistical Methodology)* 2002;**64**(4):583–39.

Suissa 2012
Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012;**67**(11):957–63.

Tricco 2015
Tricco AC, Strifler L, Veroniki AA, Yazdi F, Khan PA, Scott A, et al. Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis. *BMJ Open* 2015;**5**(10):e009183.

Trucchi 2015
Trucchi C, Paganino C, Orsi A, De Florentiis D, Ansaldi F. Influenza vaccination in the elderly: why are the overall benefits still hotly debated?. *Journal of Preventive Medicine and Hygiene* 2015;**56**(1):E37–43.

Turner 2012
Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International Journal of Epidemiology* 2012;**41**(3):818–27. [PUBMED: 22461129]

Vogelmeier 2015
Vogelmeier C, Paggiaro PL, Dorca J, Sliwinski P, Mallet M, Kirsten A, et al. Efficacy of aclidinium/formoterol fixed-dose combination versus salmeterol/fluticasone in COPD. *European Respiratory Journal* 2015;**46**(suppl 59):PA2960.

Welsh 2013
Welsh EJ, Cates CJ, Poole P. Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2013, Issue 5. DOI: 10.1002/14651858.CD007891.pub3

WHO 2016
World Health Organization. Chronic obstructive pulmonary disease. Burden of COPD. www.who.int/respiratory/copd/burden/en/ (accessed 17 December 2016).

WinBUGS [Computer program]
Medical Research Council (MRC). WinBUGS. Version 1.4.3. UK: Medical Research Council (MRC), 2007.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aaron 2007

Methods	**Design:** randomised, double-blind, placebo-controlled, parallel-group trial **Duration:** 52 weeks **Location:** 27 Canadian medical centres
Participants	**Population:** 304 adults, with a clinical history of moderate or severe COPD as defined by ATS and GOLD criteria, were randomised to 1. tiotropium + salmeterol (148) 2. tiotropium (156) **Baseline characteristics:** mean age 68 years. COPD severity moderate-severe with mean FEV1 predicted of 38%. 56% men **Inclusion criteria:** at least 1 exacerbation of COPD that required treatment with systemic corticosteroids or antibiotics within the 12 months before randomisation; age > 35 years; a history of $\geq$ 10 pack-years of cigarette smoking; documented chronic airflow obstruction, with an FEV1/FVC ratio $\leq$ 0.70 and a post-bronchodilator FEV1 < 65% of the predicted value **Exclusion criteria:** history of physician-diagnosed asthma before 40 years of age; history of physician-diagnosed chronic congestive heart failure with known persistent severe left ventricular dysfunction; people receiving oral prednisone; people with a known hypersensitivity or intolerance to tiotropium, salmeterol, or fluticasone-salmeterol; history of severe glaucoma or severe urinary tract obstruction, previous lung transplantation or lung volume reduction surgery, or diffuse bilateral bronchiectasis; and people who were pregnant or were breastfeeding
Interventions	**Inhaler device** 1. tiotropium + salmeterol: tiotropium 18 μg once daily using a HandiHaler + salmeterol 25 μg/puff, 2 puffs twice daily using a pressurised metered-dose inhaler using a spacer device 2. tiotropium + placebo: tiotropium, 18 μg once daily, + placebo inhaler, 2 puffs twice daily **Allowed co-medications:** as-needed albuterol**,** antileukotrienes, and methylxanthines
Outcomes	**Primary:** proportion of participants with $\geq$ 1 exacerbation of COPD **Secondary:** mean number of COPD exacerbations per patient-year; total number of exacerbations that resulted in urgent visits to a healthcare provider or emergency department; the number of hospitalisations for COPD; the total number of hospitalisations for all causes; changes in health-related QoL, dyspnoea, lung function
Notes	**Funding:** Canadian Institutes of Health Research and OntarioThoracic Society **Identifiers:** ISRCTN29870041

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Randomisation was done through central allocation of a randomisation schedule that was prepared from a computer-generated random listing of the 3 treatment allocations, blocked in variable blocks of 9 or 12 and stratified by site
Allocation concealment (selection bias)	Low risk	Randomisation was done through central allocation of a randomisation schedule that was prepared from a computer-generated random listing of the 3 treatment allocations, blocked in variable blocks of 9 or 12 and stratified by site
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assembled data from the visit for the suspected exacerbation were presented to a blinded adjudication committee for review, and the committee confirmed whether the encounter met the study definition of COPD exacerbation. The statistician who performed the analysis was initially blinded to patient group assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of people who stopped drug therapy was high but even in both groups. 74 (47%) participants withdrew from the tiotropium + placebo group and 64 (43%) participants on salmeterol + tiotropium group but the breakdown for withdrawal was similar between tiotropium vs tiotropium + salmeterol arms
Selective reporting (reporting bias)	Low risk	The study reported results for all listed primary and secondary outcomes

Agusti 2014

Methods	**Design:** a randomized, double-blind, double-dummy, multicentre, parallel-group study **Duration:** 12 weeks **Location:** Belgium, France, Germany, Italy, Philippines, Poland, Russian Federation, Spain, Ukraine

Participants	**Population** 1. Fluticasone propionate/salmeterol (500/50 μg) 262 2. Fluticasone furoate/vilanterol (100/25 μg) 266 **Baseline characteristics:** age 62.9 (SD 8.59) female:male 95:433 **Inclusion criteria** Adults aged > 40 years, with a smoking history of o10 pack-years and a postbronchodilator FEV1/FVC ratio of < 0.70 and a FEV1 < 70% predicted. Patients had to have experienced at least one moderate COPD exacerbation (requiring treatment with oral corticosteroid/antibiotic) or severe exacerbation (leading to hospitalisation) within the past 3 years **Exclusion criteria** A current diagnosis of asthma, serious underlying disease or infections, hospitalisation due to COPD within 12 weeks of screening, or acute worsening of COPD (defined as use of corticosteroids or antibiotics) within 6 weeks of screening
Interventions	1. Fluticasone furoate 100 μg/vilanterol 25 μg once daily 2. Fluticasone propionate 500 μg/salmeterol 50 μg twice daily **Inhaler device:** ELLIPTA DPI **Allowed co-medications:** salbutamol as needed, ipratropium, mucolytics
Outcomes	**Primary:** CFB trough in 24-h weighted-mean FEV1 on treatment day 84
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01342913, 113107

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study used an interactive voice-response system as a means for central allocation of drug in accordance with the randomisation schedule
Allocation concealment (selection bias)	Low risk	The study used an interactive voice-response system as a means for central allocation of drug in accordance with the randomisation schedule
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator and treating physician were blinded till an emergency arose

[Agusti 2014](#) *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively low in both included groups (6.1 % in salmeterol/fluticasone propionate and 8.65 in fluticasone furorate/vilanterol group)
Selective reporting (reporting bias)	Low risk	Trial registration located. Outcomes well reported

Anzueto 2009

Methods	**Design:** randomised, double-blind, parallel-group, multicentre study **Duration:** 52 weeks (+ 4-week run-in) **Location:** 98 centres in the USA and Canada
Participants	**Population:** 797 participants were randomised to 1. salmeterol alone (403) 2. salmeterol/fluticasone combination therapy (394) **Baseline characteristics** Age (mean years): salmeterol 65.3, salmeterol/fluticasone 65.4 % male: salmeterol 57, salmeterol/fluticasone 51 % FEV1 predicted (pre bronchodilator): salmeterol 33.9, salmeterol/fluticasone 34.1 Pack-years (mean): salmeterol 56.5, salmeterol/fluticasone 57.8 **Inclusion criteria:** > 40 years of age with a diagnosis of COPD, history of cigarette smoking 10 pack-years, a pre-albuterol FEV1/FVC 0.70, a FEV 150% of predicted normal and a documented history of ≥ 1 COPD exacerbations the year prior to the study that required treatment with antibiotics, OCS, and/or hospitalisation **Exclusion criteria:** current diagnosis of asthma, a respiratory disorder other than COPD, historical or current evidence of a clinically significant uncontrolled disease, or had a COPD exacerbation that was not resolved at screening
Interventions	1. Salmeterol 50 μg twice daily (LABA) 2. Salmeterol/fluticasone 50/250 μg twice daily (LABA/ICS **Inhaler device**: Diskus **Allowed co-medications:** as-needed albuterol was provided for use throughout the study. As-needed ipratropium was not provided; however, it could be used during the study. The use of concurrent inhaled long-acting bronchodilators (beta2-agonist and anticholinergic), ipratropium/albuterol combination products, oral beta-agonists, ICS, leukotriene modifiers, inhaled nedocromil and cromolyn, theophylline preparations, ritonavir and other investigational medications were not allowed during the treatment period. OCS and antibiotics were allowed for the acute treatment of a COPD exacerbation
Outcomes	Annual rate of moderate/severe exacerbations, time to first moderate/severe exacerbation, the annual rate of exacerbations requiring OCS, and pre-dose FEV1. Diary records and health status measured on the SGRQ
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT00115492, GSK NCT00115492

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The study used an interactive voice-response system as a means for central allocation of drug in accordance with the randomisation schedule
Allocation concealment (selection bias)	Low risk	The study used an interactive voice-response system as a means for central allocation of drug in accordance with the randomisation schedule
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind (assumed participants and personnel/investigators)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator and treating physician were blinded till an emergency arose
Incomplete outcome data (attrition bias) All outcomes	High risk	The withdrawal rates were very high, 39% discontinued in salmeterol arm and 32% in salmeterol/fluticasone arm. More participants were withdrawn due to lack of efficacy and exacerbation with salmeterol/fluticasone arm compared with salmeterol arm (8.2% vs 5.3%)
Selective reporting (reporting bias)	Low risk	Study reported all outcomes stated in the protocol

Asai 2013

Methods	**Design:** multicentre, randomised, open-label, parallel-group study **Duration:** 52 weeks **Location:** 35 centres in Japan
Participants	**Population** 1. Indacaterol/glycopyrrolate 110 μg/50 μg (QVA149) (119) 2. Tiotropium (39) **Baseline characteristics:** age 69.3 (SD 6.8), female:male 95.6:4.4% **Inclusion criteria:** severe stable COPD (stage 2 or stage 3), a smoking history of at least 10 pack-years, postbronchodilator FEV1 $\geq$ 30% and < 80% of the predicted normal, and postbronchodilator FEV1/FVC $\leq$ 0.7 at visit 2 **Exclusion criteria:** pregnant women or nursing mothers, concomitant pulmonary disease, a history of asthma, malignancy of any organ system, certain cardiovascular comor-

	bid conditions, and alpha-1 antitrypsin deficiency
Interventions	**Inhaler device** 1. QVA149 (indacaterol/glycopyrrolate 110 μg/50 μg) once daily delivered via Concept1 2. tiotropium (18 μg once daily) delivered via HandiHaler **Allowed co-medications:** not described
Outcomes	**Primary**: number of participants with AEs, SAEs or death
Notes	**Funding:** Novartis **Identifiers:** NCT01285492, CQVA149A1301, ARISE

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was relatively low but uneven between 2 groups (14.0% in indacaterol/glycopyrrolate and 2.6 % in tiotropium group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Bateman 2013

Methods	**Design:** multicentre, randomised, double-blind, parallel-group, placebo- and active-controlled trial **Duration:** 26 weeks (+ 2-week run-in) **Location:** academic and clinical research centres in Europe, North America, South America, Asia (India, Japan, Philippines), Australia, China, South Africa and Taiwan
Participants	**Population:** 2143 participants were randomised to 1. indacaterol/glycopyrrolate (474)

	2. indacaterol (477) 3. glycopyrronium (475) 4. open-label tiotropium (483) 5. placebo (234) We did not include placebo arm in this analysis. **Baseline characteristics:** Age (mean years): indacaterol 63.6, glycopyrronium 64.3, tiotropium 63.5, placebo 64,4 % male: indacaterol 74.4, glycopyrronium 77.2, tiotropium 75.0, placebo 72.8 % FEV1 predicted: indacaterol 54.9, glycopyrronium 55.1, tiotropium 55.1, placebo 55.2 **Inclusion criteria:** participants were aged 40 years, had moderate-severe stable COPD (GOLD stages 2 or 3 (2008 criteria)), and a smoking history of 10 pack-years. At screening, they were required to have a post-bronchodilator FEV1 > 30% and < 80% of predicted normal and postbronchodilator FEV1/FVC $\leq$ 0.70 **Exclusion criteria:** respiratory tract infection within 4 weeks prior to visit 1; concomitant pulmonary disease; history of asthma; lung cancer or a history of lung cancer; history of certain cardiovascular comorbid conditions; known history and diagnosis of alpha-1 antitrypsin deficiency; in the active phase of a supervised pulmonary rehabilitation programme; contraindicated for inhaled anticholinergic agents and 2 agonists; other protocol-defined inclusion/exclusion criteria may apply
Interventions	1. Indacaterol 150 μg once daily (LABA) 2. Glycopyrronium 50 μg once daily (LAMA) 3. Tiotropium 18 μg once daily (LAMA): open-label 4. Placebo (placebo) **Inhaler device:** all medications were administered once daily in the morning via the Breezhaler® device except for tiotropium, which was administered open-label via the HandiHaler® device **Allowed co-medications:** participants remained on a stable dose of ICS and salbutamol/albuterol was available for use as rescue medication throughout the study
Outcomes	Trough FEV1, dyspnoea, health status measured on the SGRQ score, rescue medication use and safety
Notes	**Funding:** Novartis **Identifiers:** NCT01202188

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No specific details of sequence generation but done electronically and presumed valid
Allocation concealment (selection bias)	Low risk	Eligible patients were assigned a randomisation number via Interactive Response Technology (IRT), linking the patient to a treatment arm and specific unique med-

		ication number for the study drug. The randomisation number was not communicated to the investigator contacting the IRT
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding procedures were sound, but tiotropium was delivered open-label which introduced bias for these comparisons. Blinding of participants, investigator staff, personnel performing assessments and data analysts was maintained by ensuring randomisation data remained strictly confidential and inaccessible to anyone involved in the study until the time of unblinding. In addition, the identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, and schedule of administration, appearance, taste and odour. Unblinding occurred in the case of emergencies and at the conclusion of the study
Blinding of outcome assessment (detection bias) All outcomes	High risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was relatively low and even among active comparators (8.0% in indacaterol/glycopyrronium, 11.7% in indacaterol, 11.2% in glycopyrronium, and 8.7% in tiotropium) and more than 99% were included in the analysis
Selective reporting (reporting bias)	Low risk	Prospectively registered and well reported with additional online supplemental material available

BI 205.137 2001

Methods	See Brusasco 2003
Participants	**Population:** 385 participants were randomised to salmeterol (192) and tiotropium (193) See Brusasco 2003
Interventions	See Brusasco 2003
Outcomes	See Brusasco 2003
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT02173691

BI 205.137 2001 (*Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	See Brusasco 2003
Allocation concealment (selection bias)	Low risk	See Brusasco 2003
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See Brusasco 2003
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See Brusasco 2003
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Brusasco 2003
Selective reporting (reporting bias)	Low risk	See Brusasco 2003

Bogdan 2011

Methods	**Design:** randomised, double-blind, placebo-controlled, parallel-group, multinational, phase 3, efficacy and safety study **Duration:** 12 weeks **Location:** Bulgaria, Japan, Romania, Russian Federation, Ukraine
Participants	**Population** 1. Formoterol 4.5 μg twice daily (206) 2. Formoterol 9 μg twice daily (199) **Baseline characteristics:** age 66.75 years (SD 9.4), female:male 74:539 **Inclusion criteria** • Men or women aged > 40 with a clinical diagnosis of COPD and current COPD symptoms • Current or previous smoker with a smoking history of 10 or more pack-years • Lung function parameters: FEV1/FVC $\leq$ 70%, post-bronchodilator and post-bronchodilator FEV1 < 80% of predicted normal value **Exclusion criteria** • History and/or current clinical diagnosis of asthma or atopic diseases such as allergic rhinitis • Use of inhaled glucocorticosteroids within 4 weeks prior to visit 2 • Any relevant cardiovascular disorder as judged by the investigator or any current respiratory tract disorder other than COPD

Bogdan 2011 *(Continued)*

Interventions	**Inhaler device** 1. Formoterol Turbuhaler 4.5 μg 2. Formoterol Turbuhaler 9 μg 3. Turbuhaler placebo **Allowed co-medications:** salbutamol as rescue, short-acting anticholinergics
Outcomes	**Primary:** FEV1 (L) 60 min post-dose
Notes	**Funding:** AstraZeneca **Identifiers:** NCT00628862, D5122C00001

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was low and even between 2 groups (5.3% in formoterol 4.5 and 8.5% in formoterol 9 group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Briggs 2005

Methods	**Design:** randomised, double-blind, double-dummy, parallel-group study **Duration:** 12 weeks **Location:** 50 centres located in 8 countries, including Finland, Greece, Italy, Portugal, Sweden, Turkey, UK and USA
Participants	**Population** n = 653 1. Tiotropium: (328) 2. Salmeterol (325) **Baseline characteristics:** mean age (tiotropium: 64.2 years, salmeterol 64.6 years); gender (tiotropium 65% male, salmeterol 68% male); mean % predicted FEV1 (tiotropium 37.7%, salmeterol 37.7%); mean smoking pack-year history (tiotropium 55.6 years, sal-

	meterol 56.1 years) **Inclusion criteria:** aged ≥ 40 years, cigarette smoking history of ≥ 10 pack-years, clinical diagnosis of COPD, with FEV1 % predicted ≤ 60% and FVC ≤ 70% **Exclusion criteria:** history of asthma, allergic rhinitis, atopy or a total (absolute) blood eosinophil count ≥ 600 mm; significant medical condition that could preclude participation for the full duration of the trial or interfere with the interpretation of the study results; taking systemic corticosteroids at unstable doses or in daily doses of ≥ 10 mg (or its equivalent); using beta-blockers, cromones, or anti-leukotrienes prior to enrolment in the trial; experienced a respiratory tract infection or a COPD exacerbation within 30 days of randomisation; using oxygen for > 1 h/d and unable to refrain from its use during pulmonary function testing; actively participating in a rehabilitation programme or had completed such a programme during the previous 30 days
Interventions	1. Tiotropium, 18 μg once daily via the HandiHaler device; or 2. Salmeterol, 2 actuations of 25 μg each, twice daily via a metered-dose inhaler **Inhaler device:** HandiHaler device for tiotropium, MDI for salmeterol **Allowed co-medications:** as-needed albuterol, ICS
Outcomes	**Primary:** the co-primary efficacy outcomes were average post-dose FEV1 over 12 h and peak FEV1 after 12 weeks of treatment. Average FEV1 was estimated from the AUC from 0-12 h. **Secondary:** secondary outcomes including morning pre-dose FEV1, FEV1 at each time point over 12 h, corresponding FVC parameters, incidence and frequency of COPD exacerbations (the number or percentage of participants with at least one COPD exacerbation, time to first exacerbation, number of exacerbations, and exacerbation days), rescue medication use, and incidence of SAEs
Notes	**Funding:** Boehringer Ingelheim and Pfizer **Identifiers:** 205.264

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Boehringer Ingelheim generated the randomisation list using a validated system, which involved a pseudo-random number generator so that the resulting treatment sequence was both reproducible and non-predictable
Allocation concealment (selection bias)	Low risk	All investigational medication for each participant was identified by a unique medication number. Each eligible participant was assigned the lowest medication number available to the investigator at the time of randomisation

Briggs 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Boehringer Ingelheim was responsible for preparing and coding study medication in a blinded fashion (Boehringer Ingelheim study drug and control were indistinguishable). Participants, investigators and study personnel remained blinded with regard to the treatment assignments up to database lock
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In all studies, a selection of standard respiratory endpoints like pulmonary function, SGRQ, TDI, treadmill tolerance, and exacerbations were used. Outcome assessors remained blinded with regard to the treatment assignments up to database lock
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawal rates were relatively small and even between the groups (tiotropium 8.8%, salmeterol 12.6%)
Selective reporting (reporting bias)	Unclear risk	Unable to locate protocol

Brusasco 2003

Methods	**Design:** pooled results from 2 randomised, double-blind, double-dummy, parallel-group studies **Duration:** 6 months (+ 2-week run-in period) **Location:** studies were performed in 18 countries The only difference in the two studies was the duration of serial spirometry in the clinic (12 h in one study, 3 h in the second)
Participants	**Population:** 807 participants were randomised to 1. salmeterol (405) 2. tiotropium (402) **Baseline characteristics:** Age (mean years): salmeterol, 64.1; placebo, 64.6 % male: salmeterol, 75.1; placebo, 76.3 % FEV1 predicted: salmeterol 37.7; placebo, 38.7 Pack-years (mean): salmeterol, 44.8; placebo, 42.4 **Inclusion criteria:** participants were required to have relatively stable airway obstruction with FEV1 < 65% of predicted normal and < 70% of FVC, > 40 years of age, with a smoking history of > 10 pack-years **Exclusion criteria:** history of asthma, allergic rhinitis or atopy or with an increased total eosinophil count; use of supplemental oxygen or an upper respiratory tract infection in the 6 weeks before screening; significant disease other than COPD (significant disease was defined as a disease that, in the opinion of the investigator, would put the patient at risk because of participation in the study, or a disease that would influence the results of the study.)

Interventions	1. Salmeterol 50 μg twice daily (LABA) 2. Tiotropium 18 μg once daily (LAMA) 3. Placebo (placebo) **Inhaler device:** metered dose **Allowed co-medications:** participants were allowed to continue previously prescribed regular inhaled steroids or regular oral steroids, not exceeding a dose equivalent to approximately 10 mg prednisone daily. We could not find the number of participants taking these medications during the study
Outcomes	Mean CFB on the SGRQ and number whose score decreased by at least 4 units; exacerbations (number, time to first exacerbation); hospital admissions; FEV1; FVC; dyspnoea (evaluated using the BDI and the TDI); diary card data
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT02172287, NCT02173691, 205.130, and 205.137

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Boehringer Ingelheim generated the randomisation list using a validated system, which involved a pseudo-random number generator so that the resulting treatment sequence was both reproducible and non-predictable
Allocation concealment (selection bias)	Low risk	All investigational medication for each participant was identified by a unique medication number. Each eligible participant was assigned the lowest medication number available to the investigator at the time of randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Boehringer Ingelheim was responsible for preparing and coding study medication in a blinded fashion (Boehringer Ingelheim study drug and control were indistinguishable). Participants, investigators and study personnel remained blinded with regard to the treatment assignments up to database lock. Double-dummy technique was used to blind different application devices
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In all studies, a selection of standard respiratory endpoints like pulmonary function, SGRQ, TDI, treadmill tolerance and exacerbations were used. Outcome assessors

Brusasco 2003 (*Continued*)

		remained blinded with regard to the treatment assignments up to database lock
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawal rates were relatively even between groups (salmeterol 18.8%, tiotropium 15.4%)
Selective reporting (reporting bias)	Low risk	Results for all expected and specified outcomes were reported except for FEV1 outcome (secondary outcome), which was not reported in a way that we could include in the quantitative synthesis

Buhl 2011

Methods	**Design:** randomised, placebo-controlled, double-blind, double-dummy **Duration:** 12 weeks **Location:** 223 centres in 22 countries: Austria, Belgium, Canada, Colombia, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Mexico, Norway, Poland, Russia, Slovakia, Spain, Switzerland, Turkey, UK and USA
Participants	**Population:** n = 1598 1. Tiotropium (797) 2. Indacaterol (801) **Baseline characteristics** Mean age (tiotropium: 63.6 years, indacaterol 63.4 years); Gender (tiotropium 70% male, indacaterol 67%); Mean% predicted FEV1 (tiotropium 54.3%, indacaterol 54.6%); Mean smoking pack-year history (tiotropium 41.8 years, indacaterol 43.2 years) **Inclusion criteria:** diagnosis of COPD, smoking history of at least 10 pack-years, post-bronchodilator FEV1 $<$ 80% and $\geq$ 30%of the predicted normal value, post-bronchodilator FEV1/FVC $\leq$ 70% **Exclusion criteria:** received systemic corticosteroids or antibiotics and/or were hospitalised for a COPD exacerbation in the 6 weeks prior to screening, respiratory tract infection within 6 weeks prior to screening, concomitant pulmonary disease, history of asthma, diabetes type 1 or uncontrolled diabetes type 2, lung cancer or history of lung cancer, history of certain cardiovascular comorbid conditions
Interventions	**Inhaler device** 1. Tiotropium, 18 μg once daily via the HandiHaler device 2. Indacaterol 150 μg delivered via a single-dose DPI **Allowed co-medications:** as-needed albuterol, ICS
Outcomes	**Primary:** trough FEV1 24 h post-dose after 12 weeks of treatment **Secondary:** FEV1 AUC 5 min-4 h post-dose on day 1, week 4 and week 12. Rescue medication use over 12 weeks. Safety and tolerability

Buhl 2011 (*Continued*)

Notes	**Funding:** Novartis **Identifiers:** NCT00900731, CQAB149B2350

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study used an interactive voice-response system as a means for central allocation of drug in accordance with the randomisation schedule
Allocation concealment (selection bias)	Low risk	The study used an interactive voice-response system as a means for central allocation of drug in accordance with the randomisation schedule
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators, study staff performing the assessments and data analysts were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rates were low and even (tiotropium 7.6%, indacaterol 7.5%)
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

Buhl 2015a

Methods	**Design:** randomised, double-blind, parallel-group, multicentre **Duration:** 52 weeks **Location:** see Buhl 2015a&b
Participants	**Population:** 2624 participants 1. Tiotropium 5 μg + olodaterol 5 μg fixed-dose combination once daily 2. Tiotropium 2.5 μg + olodaterol 5 μg fixed-dose combination once daily 3. Olodaterol 5 μg once daily 4. Tiotropium 5 μg once daily 5. Tiotropium 2.5 μg once daily **Baseline characteristics:** mean age 64.2 years. COPD severity was GOLD stage 2 (FEV1 50%-80% predicted) in 50% of participants, stage 3 (30%-50% predicted) in 39% of participants, and stage 4 (< 30% predicted) in 11% of participants, with mean FEV1 of 50% predicted. 74% were men. 38% were current smokers. 48% were taking ICS. 86% had comorbidity at baseline

Buhl 2015a (*Continued*)

	Inclusion criteria: outpatients aged > 40 years with a history of moderate-very severe COPD (GOLD stage 2-4); post-bronchodilator FEV1 < 80%of predicted normal; post-bronchodilator FEV1/FVC ≤ 70%; current or ex-smokers with a smoking history of > 10 pack-years **Exclusion criteria:** clinically relevant abnormal baseline laboratory parameters or a history of asthma; MI within 1 year of screening; unstable or life-threatening cardiac arrhythmia; known active TB; clinically evident bronchiectasis; cystic fibrosis or life-threatening pulmonary obstruction; hospitalised for heart failure within the past year; diagnosed thyrotoxicosis or paroxysmal tachycardia; previous thoracotomy with pulmonary resection; regular use of daytime oxygen if people were unable to abstain during clinic visits; or currently enrolled in a pulmonary rehabilitation programme (or completed in the 6 weeks before screening)
Interventions	**Inhaler device** 1. Tiotropium 5 μg + olodaterol 5 μg fixed-dose combination via Respimat once daily 2. Tiotropium 2.5 μg + olodaterol 5 μg fixed-dose combination via Respimat once daily 3. Olodaterol 5 μg Respimat once daily 4. Tiotropium 5 μg Respimat once daily 5. Tiotropium 2.5 μg Respimat once daily **Allowed co-medications:** as-needed salbutamol, ICS, theophylline
Outcomes	**Primary:** 1. FEV1 AUC (0-3 h) response on day 169 2. Trough FEV1 response on day 170 3. SGRQ total score on day 169 from the 2 twin trials, Buhl 2015a (NCT01431274) and Buhl 2015b (NCT01431287) These outcomes were also measured at days 85 and 365
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01431274, 1237.5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Buhl 2015a&b
Allocation concealment (selection bias)	Low risk	See Buhl 2015a&b
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See Buhl 2015a&b
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Buhl 2015a&b

Incomplete outcome data (attrition bias) All outcomes	High risk	See Buhl 2015a&b
Selective reporting (reporting bias)	Low risk	See Buhl 2015a&b

Buhl 2015a&b

Methods	**Design:** randomised, double-blind, parallel-group, multicentre **Duration:** 52 weeks **Location:** 25 countries including Australia, Brazil, Canada, South Africa USA and EU countries, including UK
Participants	**Population:** 5163 participants 1. Tiotropium 5 μg + olodaterol 5 μg fixed-dose combination once daily 2. Tiotropium 2.5 μg + olodaterol 5 μg fixed-dose combination once daily 3. Olodaterol 5 μg once daily 4. Tiotropium 5 μg once daily 5. Tiotropium 2.5 μg once daily **Baseline characteristics:** see Buhl 2015a and Buhl 2015b **Inclusion criteria:** outpatients aged > 40 years with a history of moderate-very severe COPD (GOLD stages 2-4); post-bronchodilator FEV1 < 80% of predicted normal; postbronchodilator FEV1/FVC < 70%; current or ex-smokers with a smoking history of > 10 pack-years **Exclusion criteria:** clinically relevant abnormal baseline laboratory parameters or a history of asthma; MI within 1 year of screening; unstable or life-threatening cardiac arrhythmia; known active TB; clinically evident bronchiectasis; cystic fibrosis or life-threatening pulmonary obstruction; hospitalised for heart failure within the past year; diagnosed thyrotoxicosis or paroxysmal tachycardia; previous thoracotomy with pulmonary resection; regular use of daytime oxygen if people were unable to abstain during clinic visits; or currently enrolled in a pulmonary rehabilitation programme (or completed in the 6 weeks before screening)
Interventions	**Inhaler device** 1. Tiotropium 5 μg + olodaterol 5 μg fixed-dose combination via Respimat once daily 2. Tiotropium 2.5 μg + olodaterol 5 μg fixed-dose combination via Respimat once daily 3. Olodaterol 5 μg Respimat once daily 4. Tiotropium 5 μg Respimat once daily 5. Tiotropium 2.5 μg Respimat once daily **Allowed co-medications:** as-needed salbutamol, ICS, theophylline
Outcomes	**Primary:** 1. FEV1 AUC (0-3 h) response on day 169 2. Trough FEV1 response on day 170 3. SGRQ total score on day 169 from the 2 twin trials, Buhl 2015a (NCT01431274) and Buhl 2015b (NCT01431287). These outcomes were also measured at days 85 and 365

Buhl 2015a&b (*Continued*)

Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01431274, NCT01431287, 1237.5, 1237.6

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study used an interactive voice-response system as a means for central allocation of drug in accordance with the randomisation schedule
Allocation concealment (selection bias)	Low risk	The study used an interactive voice-response system as a means for central allocation of drug in accordance with the randomisation schedule
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind for all arms
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrwal was uneven among comparators of interest (18.3% in olodaterol 5, 13.7% in tiotropium 5 and 10.7% in tiotropium/olodaterol 5/5 arms)
Selective reporting (reporting bias)	Low risk	Prospectively registered and well reported

Buhl 2015b

Methods	**Design:** randomised, double-blind, parallel-group, multicentre **Duration:** 52 weeks **Location:** see Buhl 2015a&b
Participants	**Population:** 2539 participants 1. Tiotropium 5 μg + olodaterol 5 μg fixed-dose combination once daily 2. Tiotropium 2.5 μg + olodaterol 5 μg fixed-dose combination once daily 3. Olodaterol 5 μg once daily 4. Tiotropium 5 μg once daily 5. Tiotropium 2.5 μg once daily **Baseline characteristics:** mean age 63.8 years COPD severity was GOLD stage 2 (FEV1 50%-80% predicted) in 50% of participants, stage 3 (30%-50% predicted) in 38%, and stage 4 (< 30% predicted) in 12% of participants, with mean FEV1 of 50% predicted. 72% were men. 36% were current smokers.

	47% were taking ICS. 87% had comorbidity at baseline **Inclusion criteria:** outpatients aged > 40 years with a history of moderate-very severe COPD (GOLD stage 2-4); post-bronchodilator FEV1 < 80% of predicted normal; postbronchodilator FEV1/FVC ≤ 70%; current or ex-smokers with a smoking history of > 10 pack-years **Exclusion criteria:** clinically relevant abnormal baseline laboratory parameters or a history of asthma; MI within 1 year of screening; unstable or life-threatening cardiac arrhythmia; known active TB; clinically evident bronchiectasis; cystic fibrosis or life-threatening pulmonary obstruction; hospitalised for heart failure within the past year; diagnosed thyrotoxicosis or paroxysmal tachycardia; previous thoracotomy with pulmonary resection; regular use of daytime oxygen if people were unable to abstain during clinic visits; or currently enrolled in a pulmonary rehabilitation programme (or completed in the 6 weeks before screening)
Interventions	**Inhaler device** 1. Tiotropium 5 μg + olodaterol 5 μg fixed-dose combination via Respimat once daily 2. Tiotropium 2.5 μg + olodaterol 5 μg fixed-dose combination via Respimat once daily 3. Olodaterol 5 μg Respimat once daily 4. Tiotropium 5 μg Respimat once daily 5. Tiotropium 2.5 μg Respimat once daily **Allowed co-medications:** as-needed salbutamol, ICS, theophylline
Outcomes	**Primary:** 1. FEV1 AUC (0-3 h) response on day 169 2. Trough FEV1 response on day 170 3. SGRQ total score on day 169 from the 2 twin trials, Buhl 2015a (NCT01431274) and Buhl 2015b (NCT01431287) These outcomes were also measured at days 85 and 365
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01431287, 1237.6

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Buhl 2015a&b
Allocation concealment (selection bias)	Low risk	See Buhl 2015a&b
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See Buhl 2015a&b

Buhl 2015b *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Buhl 2015a&b
Incomplete outcome data (attrition bias) All outcomes	High risk	See Buhl 2015a&b
Selective reporting (reporting bias)	Low risk	See Buhl 2015a&b

Buhl 2015c

Methods	**Design:** multicentre, randomised, parallel-group, blinded study **Duration:** 26 weeks **Location:** Germany
Participants	**Population** 1. Indacaterol/glycopyrronium 110/50 μg (476) 2. Tiotropium 18 μg + formoterol 12 μg (458) **Baseline characteristics:** age 62.9 (SD 8.29) female:male 319:615 **Inclusion criteria** 1. Male or female adults aged $\geq$ 40 years 2. Moderate-severe COPD (GOLD 2010) 3. Smoking history of at least 10 pack-years 4. Post-bronchodilator FEV1 < 80% and $\geq$ 30% of the predicted normal value and post-bronchodilator FEV1/FVC $\leq$ 70% **Exclusion criteria** • Pregnant women or nursing mothers or women of child-bearing potential not using adequate contraception • History of long QT syndrome • Type 1 or uncontrolled type 2 diabetes • COPD exacerbation or respiratory tract infection within 6 weeks prior to screening • History of asthma • Pulmonary lobectomy, lung volume reduction surgery, or lung transplantation • Concomitant pulmonary disease • Requiring LTOT (> 15 h/d)
Interventions	**Inhaler device** 1. QVA149 (indacaterol/glycopyrronium) 110/50 µg a single-dose DPI 2. Tiotropium proprietary inhaler (HandiHaler) 3. formoterol capsules Aerolizer device **Allowed co-medications:** salbutamol as a rescue and ICS
Outcomes	**Primary:** SGRQ-C total score after 26 weeks of treatment (non-inferiority analysis)
Notes	**Funding:** Novartis **Identifiers:** NCT01574651, CQVA149ADE01

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A validated system that automated the random assignment of treatment arms to randomisation numbers in the specified ratio
Allocation concealment (selection bias)	Low risk	A validated system that automated the random assignment of treatment arms to randomisation numbers in the specified ratio
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator staff, personnel performing assessments, and data analysts remained blinded from randomisation until database lock
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively low in both included groups (12.8 % in indacaterol/glycopyrronium and 11.4% in tiotropium + formoterol)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Calverley 2003

Methods	**Design:** randomised, double-blind, placebo-controlled, parallel-group study **Duration:** 52 weeks (+ 2-week run-in) **Location:** 109 centres in 15 countries or regions
Participants	**Population:** 1022 participants were randomised to 1. formoterol (255) 2. budesonide (257) 3. formoterol/budesonide combination (254) 4. placebo (256) **Baseline characteristics:** Mean age (years): formoterol 63, budesonide 64, formoterol/budesonide 64, placebo 65 % male: formoterol 75, budesonide 74, formoterol/budesonide 78, placebo 75 % FEV1 predicted: formoterol 36, budesonide, formoterol/budesonide, placebo 36 Pack-years: formoterol 38, budesonide 39, formoterol/budesonide 39, placebo 39 **Inclusion criteria:** men and women > 40 years old; history of at least 10 pack-years; COPD for at least 2 years; ≤ 70% FEV1/FVC, FEV1 < 50% predicted; ≥ 1 COPD exacerbations requiring medication in previous 2-12 months

	Exclusion criteria: history of asthma or seasonal allergic rhinitis before age 40; any relevant cardiovascular disorders or other disease
Interventions	1. Formoterol 9 µg twice daily (LABA) 2. Budesonide 400 µg twice daily (ICS) 3. Formoterol/budesonide 9/320 µg twice daily (LABA/ICS) 4. Placebo (placebo) **Inhaler device:** DPI **Allowed co-medications:** terbutaline (0.5 mg) as needed; maximum 3-week course of OCS and antibiotics were allowed in the event of exacerbations; parenteral steroids and/or nebulised treatment were allowed at emergency visits Medications excluded during the study period were oxygen therapy; beta-blocking agents; ICSs; disodium cromoglycate; leukotriene antagonists or 5-lipoxygenase inhibitors; other bronchodilators; antihistamines and medications containing ephedrine
Outcomes	SGRQ, COPD exacerbations, FEV1, FVC, morning and evening PEF, diary card data
Notes	**Funding:** AstraZeneca **Identifiers:** SD-039-0670

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised to treatment. No details of sequence generation methods but assumed to adhere to usual AstraZeneca methods
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study reported as double-blind (participants and investigators)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No subjective assessor-rated outcomes were reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal was high and uneven in the arms of interest (formoterol, 43.5%; budesonide/formoterol 29.1%). Study used ITT analysis and all hypothesis testing but no information regarding method of imputation was provided
Selective reporting (reporting bias)	Low risk	Could not locate protocol but all relevant outcomes were reported

Calverley 2003 TRISTAN

Methods	**Design:** randomised, double-blind, placebo-controlled, parallel-group design **Duration:** 52 weeks (+ 2-week run-in period) **Location:** 196 centres in 25 countries
Participants	**Population:** 1466 participants were randomised to 1. salmeterol (372) 2. fluticasone (375) 3. salmeterol/fluticasone combination (358) 4. placebo (361) **Baseline characteristics:** Mean age (years): salmeterol 63.2, fluticasone 63.5, salmeterol/fluticasone 62.7, placebo 63.4 % male: salmeterol 70, fluticasone 69.5, salmeterol/fluticasone 75.4, placebo 75 % FEV1 predicted: salmeterol 44.3, fluticasone 45.0, salmeterol/fluticasone 44.8, placebo 44.2 Pack-years: salmeterol 43.7, fluticasone 41.5, salmeterol/fluticasone 42.0, placebo 43.4 **Inclusion criteria:** 10-pack-year history of cigarette smoking; a history of cough productive of sputum on most days for at least 3 months of the year, for at least 2 years; documented history of COPD exacerbations each year for the previous 3 years, including at least 1 exacerbation in the last year that required oral corticosteroids and/or antibiotics; a baseline (pre-bronchodilator) FEV1 25% to 70% of predicted normal; poor reversibility of airflow obstruction (defined as an increase < 10% of predicted normal FEV1 value 30 min after inhalation of 400 μg salbutamol) and FEV1/FVC ratio $\leq$ 70% **Exclusion criteria:** respiratory disorders other than COPD; received systemic corticosteroids, high doses of ICS or antibiotics in the 4 weeks before the 2-week run-in
Interventions	1. Salmeterol 50 µg twice daily (LABA) 2. Fluticasone 500 µg twice daily (ICS) 3. Salmeterol/fluticasone 50/500 µg twice daily (LABA/ICS) 4. Placebo (placebo) **Inhaler device:** multi-dose dry powder **Allowed co-medications:** inhaled salbutamol was used as relief medication throughout the study, and regular treatment with anticholinergics, mucolytics and theophylline was allowed. Medications not allowed during the study period were ICSs and LABAs
Outcomes	SGRQ, COPD exacerbations, FEV1 (at least 6 h after medication), pretreatment FVC and post-bronchodilator FEV1 and FVC, morning PEF, diary card data
Notes	**Funding:** GlaxoSmithKline **Identifiers:** SFCB3024

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	We used a randomisation schedule generated by the patient allocation for clinical trials program to assign patients to study treatment groups

Calverley 2003 TRISTAN (*Continued*)

Allocation concealment (selection bias)	Low risk	Every participating centre was supplied with a list of participant numbers (assigned to patients at their first visit) and a list of treatment numbers. Patients who satisfied the eligibility criteria were assigned the next sequential treatment number from the list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drugs were labelled in away to ensure that both the participant and the investigator were unaware of the allocated treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No subjective assessor-rated outcomes and investigators remained blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal relatively even but high in both groups (salmeterol 32.0%, placebo 38.8%) but the ITT population, consisting of all participants who were randomised to treatment and received at least 1 dose of the study medication, was used for all analyses of efficacy and safety. Unclear what method of imputation was used for each outcome
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported in detail.

Calverley 2007

Methods	**Design:** multicentre, randomised, double-blind, parallel-group, placebo-controlled study **Duration:** 3 years (156 weeks), (+ 3-week run-in period) **Location:** 466 centres in 42 countries comprising 190 centres in USA, 134 centres in Western Europe, 46 centres in Eastern Europe, 37 centres in Asia Pacific, and 59 centres in other regions
Participants	**Population:** 6184 participants were randomised to 1. salmeterol (1542) 2. fluticasone (1551) 3. salmeterol/fluticasone combination (1546) 4. placebo (1545) **Baseline characteristics:** Mean age (years): salmeterol 65.1, fluticasone 65.0, salmeterol/fluticasone 65.0, placebo 65.0 % male: salmeterol 76.3, fluticasone 75.4, salmeterol/fluticasone 75.1, placebo 76.3 % FEV1 predicted: salmeterol 43.6, fluticasone 44.1, salmeterol/fluticasone 44.3, placebo 44.1 Pack-years: salmeterol 49.3, fluticasone 49.2, salmeterol/fluticasone 47.0, placebo 48.6

	Inclusion criteria: male or female current or former smokers; history of at least 10 pack-years; clinical diagnosis of COPD; aged 40-80 years inclusive, with pre-bronchodilator FEV1 < 60% predicted at entry to the study **Exclusion criteria:** current diagnosis of asthma; current respiratory disorders other than COPD; lung volume reduction surgery and/or transplant; serious uncontrolled disease; evidence of alcohol, drug or solvent abuse; hypersensitivity to ICS, bronchodilators or lactose; deficiency of alpha1-antitrypsin; exacerbation during run-in period
Interventions	1. Salmeterol 50 µg twice daily (LABA) 2. Fluticasone 500 µg twice daily (ICS) 3. Salmeterol/fluticasone 50/500 µg twice daily (LABA/ICS) 4. Placebo (placebo) **Inhaler device:** multi-dose dry powder **Allowed co-medications:** Ventolin as relief, inhaled long-acting bronchodilators and long-term OCS (theophyllines long- and short-acting, SABAs and short-acting anti-cholinergic agents allowed) Medications not allowed during the study period were ICS, inhaled long-acting bronchodilators, long-term OCS and LTOT
Outcomes	SGRQ, COPD exacerbations, adjusted mean change FEV1
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT0026821, GSK SCO30003, TORCH

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from protocol: "Subjects will be assigned to study treatment in accordance with the randomisation schedule, which will be generated using the GW computer program Patient Allocation for Clinical Trials."
Allocation concealment (selection bias)	Low risk	Quote from protocol: "Subjects will be centrally randomised to one of the four treatment groups via the System for Central Allocation of Drug and will be stratified by smoking status"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote from protocol: "Once the database has been frozen, the treatment allocations will be unblinded and all of the analyses detailed in this document will be performed. The treatment allocations will be unblinded using standard GSK systems. The database will be frozen by BDS Respiratory Data Management, GSK"

Calverley 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent clinical end point committee, whose members were unaware of the treatment assignments, determined the primary cause of death and whether death was related to COPD. No other outcomes were assessor-rated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rates quite similar but both high by the end of the 36-month treatment period. Acceptable methods of imputation used in all cases. For any participant who withdraws prematurely from the study, all available data up to the time of discontinuation were included in the analyses. Mortality data were collected for participants who withdrew early
Selective reporting (reporting bias)	Low risk	All relevant outcomes stated in the protocol were reported in detail

Calverley 2010

Methods	**Design**: double-blind, double-dummy, randomised, active-controlled, parallel-group study **Duration**: 48 weeks (+ 4 week run-in) **Location**: conducted at 76 centres in 8 countries across Europe
Participants	**Population**: 718 participants were randomised to 1. formoterol (239) 2. formoterol/budesonide combination (242) 3. formoterol/beclomethasone combination (237) **Baseline characteristics** Age (mean years): budesonide/formoterol 64.1, formoterol 63.7 % male: budesonide/formoterol 81.5, formoterol 81.1 % FEV1 predicted: budesonide/formoterol 42.3, formoterol 42.5 Pack-years (mean): budesonide/formoterol 37.8, formoterol 39.7 **Inclusion criteria**: hospital outpatients with severe stable COPD according to the GOLD criteria; aged 40 years with a diagnosis of symptomatic COPD for > 2 years, at least a 20 pack-years smoking history, a post-bronchodilator FEV1 between 30% and 50% of the predicted normal and at least 0.7 L absolute value and a pre-dose FEV1/FVC of 0.7; at least 1 exacerbation requiring medical intervention (OCS and/or antibiotic treatment and/or need for a visit to an emergency department and/or hospitalisation) within 2-12 months before the screening visit and to be clinically stable for the 2 months before study entry; change in FEV1 < 12% of predicted normal value 30 min following inhalation of 200 μg of salbutamol MDI **Exclusion criteria:** history of asthma, allergic rhinitis or other atopic disease, variability of symptoms from day to day and frequent symptoms at night and early morning (suggestive of asthma); receiving LTOT or they had a lower respiratory tract infection or had been

	hospitalised for an acute COPD exacerbation within 2 months before screening or during the run-in period. Treatment with oral, injectable or depot corticosteroids and antibiotics, long-acting antihistamines or changes in the dose of an oral modified release theophylline in the 2 months preceding screening and during the run-in period were excluded
Interventions	1. Formoterol 12 µg twice daily (LABA) 2. Formoterol/budesonide 12/400 µg twice daily (LABA/ICS) **Inhaler device:** DPI **Allowed co-medications**: not described
Outcomes	Change in pre-dose morning FEV1 and mean rate of COPD exacerbations per participant per year, FVC, PEF, SGRQ total score, 6MWD, BMI, BODE index, safety evaluations including ECG
Notes	**Funding**: Chiesi Farmaceutici **Identifier(s)**: NCT00476099

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation scheme followed a balanced-block centre-stratified design and was prepared via a computerised system
Allocation concealment (selection bias)	Low risk	Participants were centrally assigned, in each centre, to one of the 3 treatment arms at the end of the run-in period through an Interactive Voice/Web Response System (IXRS)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	On each study day, participants took both active medications and matched placebo twice daily, in order to maintain blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	On each study day, participants took both active medications and matched placebo twice daily, in order to maintain blinding. In case of emergency, un-blinding of the treatment code was done through IXRS
Incomplete outcome data (attrition bias) All outcomes	Low risk	12.3% withdrew from the combination group and 14.2% from the formoterol group. Judged to be relatively low and even between groups, and the ITT population were used using last observation carried forward

Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

Cazzola 2007

Methods	**Design:** double-blind, double-dummy, randomised, parallel-group design **Duration:** 12 weeks **Location:** Italy
Participants	**Population** 90 participants were randomised to 1. Fluticasone propionate/salmeterol 500/50 µg (30) 2. Tiotropium 18 µg (30) 3. Fluticasone propionate/salmeterol + tiotropium (30) - not included in this review. **Baseline characteristics:** age 65.3. female:male 6:54 **Inclusion criteria:** aged ≥ 50 years, and were current or former smokers with a ≥ 20 pack-year history. A baseline FEV1 < 50% of predicted, and a post-bronchodilator FEV1/FVC ≤ 70% following salbutamol 400 µg **Exclusion criteria:** current evidence of asthma as primary diagnosis; unstable respiratory disease requiring oral/parenteral corticosteroids within 4 weeks prior to study entry; upper or lower respiratory tract infection within 4 weeks of the screening visit; unstable angina or unstable arrhythmias; concurrent use of medications that affected COPD; and evidence of alcohol abuse
Interventions	**Inhaler device** 1. Fluticasone propionate/salmeterol 500/50 µg Diskus 2. Tiotropium 18 µg HandiHaler **Allowed co-medications:** salbutamol as rescue and theophylline
Outcomes	**Primary:** mean CFB in predose FEV1 after 3-month treatment
Notes	**Funding:** none reported **Identifiers:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to receive FSC, tiotropium or their combination by a computer-generated list
Allocation concealment (selection bias)	Low risk	Participants were randomised to receive FSC, tiotropium or their combination by a computer-generated list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Cazzola 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was low and even between included groups
Selective reporting (reporting bias)	Unclear risk	Unable to locate protocol to check outcome reporting

Chapman 2014

Methods	**Design:** a randomised, blinded, double-dummy, parallel-group study **Duration:** 12 weeks **Location:** Canada, Croatia, Czech Republic, Estonia, France, Germany, Guatemala, India, Republic of Korea, Latvia, Lithuania, Philippines, Poland, South Africa, Taiwan
Participants	**Population** 1. Glycopyrronium 50 µg (123) 2. Tiotropium 18 µg (40) **Baseline characteristics:** age 63.5 (SD 8.0), female:male 172:485 **Inclusion criteria** • Moderate-severe stable COPD (stage 2 or stage 3) according to the current GOLD 2010 criteria • Post-bronchodilator FEV1 $\geq$ 30% and < 80% of the predicted normal, and a post-bronchodilator FEV1/FVC < 0.70 at screening • Current or ex-smokers who have a smoking history of at least 10 pack-years (e.g. 10 pack years = 1 pack/day x 10 years, or ½ pack/day x 20 years). • Symptomatic patients, according to daily electronic diary data between visit 2 (day -14) and visit 3 (day 1), with a total score of $\geq$ 1 on at least 4 of the last 7 days prior to visit 3 **Exclusion criteria** • Pregnant or nursing (lactating) women • Clinically relevant laboratory abnormality or a clinically significant condition before visit 1 (in the judgment of the investigator, or the responsible Novartis personnel) • Narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or moderate-severe renal impairment or urinary retention. (BPH patients who are stable on treatment can be considered) • Receiving medications in the classes listed in the protocol as prohibited
Interventions	**Inhaler device** 1. NVA237 (glycopyrronium) 50 μg inhalation capsules once daily, delivered via DPI 2. Tiotropium 18 μg once daily delivered via HandiHaler device **Allowed co-medications:** salbutamol/albuterol as rescue
Outcomes	**Primary:** trough FEV1 after 12 weeks of treatment

Chapman 2014 *(Continued)*

Notes	**Funding:** Novartis **Identifiers:** NCT01613326, CNVA237A2314

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study used an automated, interactive, voice-response technology
Allocation concealment (selection bias)	Low risk	Study used an automated, interactive, voice-response technology
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation data were kept strictly confidential until the time of unblinding, and were not accessible by anyone involved in the conduct of the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was low and even between two groups (4.0% in glycopyrronium and 4.2% in tiotropium group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

COMBINE 2017

Methods	**Design:** randomised, open-label, parallel-group, 2-treatment arm, active-controlled, fixed-dose, phase 4, clinical study **Duration:** 24 weeks **Location:** Argentina, Brazil, Chile, Dominican Republic, Ecuador, Honduras, Mexico, Panama
Participants	**Population** 242 participants were randomised to 1. Fluticasone propionate + salmeterol (133) 2. Budesonide + indacaterol (109) **Baseline characteristics:** age 67.2 (SD 8.7) female:male 95:127 **Inclusion criteria** 1. Outpatients with stable COPD groups C and D according to the GOLD 2011 definition 2. Current or ex-smokers who have a smoking history of at least 10 pack-years 3. History of at least 1 exacerbation **Exclusion criteria** 1. History or current diagnosis of ECG abnormalities

	2. Diabetes type 1 or uncontrolled diabetes type 2 including patients with a history of blood glucose levels consistently outside the normal range 3. BMI > 40 kg/m2 4. Lung cancer or a history of lung cancer 5. History of malignancy of any organ system 6. Uncontrolled or unstable, on permitted therapy, who in the opinion of the investigator, have clinically significant renal, cardiovascular, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or haematological abnormalities which could interfere with the assessment of the efficacy and safety of the study treatment 7. Requiring oxygen therapy for chronic hypoxaemia 8. Respiratory tract infection within 6 weeks prior to visit 1 9. Concomitant pulmonary disease, e.g. pulmonary TB, bronchiectasis, sarcoidosis, interstitial lung disorder or pulmonary hypertension 10. Known diagnosis of alpha-1 antitrypsin deficiency 11. History of lung surgery
Interventions	1. Budesonide + indacaterol 2. Fluticasone + salmeterol **Inhaler device** 1. Budesonide 400 μg twice daily via Breezhaler device 2. Fluticasone 250 μg twice daily via Accuhaler device 3. Indacaterol 150 μg once daily via Breezhaler device 4. Salmeterol 50 μg twice daily via Diskus device **Allowed co-medications:** “rescue medication” as needed
Outcomes	**Primary:** CFB in Trough FEV1 (Non-inferiority Analysis)
Notes	**Funding:** Novartis **Identifiers:** NCT02055352, CQAB149BAR01

Risk of bias

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label

Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was relatively low but uneven between two groups (5.5% in budesonide/formoterol and 15% in fluticasone propionate/salmeterol)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

COSMOS-J 2016

Methods	**Design:** multicentre, randomised, double-dummy study **Duration:** 24 weeks **Location:** 39 sites in Japan
Participants	**Population** 1. Fluticasone propionate/salmeterol 250/50 µg (136) 2. Tiotropium 18 µg (126) **Baseline characteristics:** age 68.3 (SD 7.02), female:male 20:385 **Inclusion criteria** 1. Male or female aged 40-80 years inclusive 2. Established clinical history of COPD (defined as per the GOLD definition) 3. Achieves a grade of ≥ 1 on mMRC at visit 1 4. Post-bronchodilator FEV1 of ≥ 30% to ≤ 80% of predicted normal 5. Post-bronchodilator FEV1/FVC ratio < 70% 6. Current or ex-smoker with a smoking history of > 10 pack-years. Ex-smokers are required to have stopped smoking ≥ 6 months prior to visit 1. Ex-smokers who stopped smoking < 6 months ago will be defined as current smokers. 7. QTc < 450 msec at visit 1; or for participants with bundle branch block QTc should be < 480 msec **Exclusion criteria** 1. Predominant asthma (comorbid asthma is not an exclusion criteria) 2. Medical diagnosis of narrow-angle glaucoma, prostatic hyperplasia or bladder neck obstruction that in the opinion of the investigator should prevent them from entering the study. 3. Known respiratory disorders other than COPD (e.g. lung cancer, sarcoidosis, TB or lung fibrosis) 4. Has undergone lung surgery e.g. lung transplant and/or lung volume reduction 5. Had a chest X-ray indicating diagnosis other than COPD that might interfere with the study (chest X-ray to be taken at visit 1, if participant has not had one and/or CT image taken within 3 months of visit 1) 6. Requires regular (daily) or LTOT. (LTOT is defined as ≥ 12 h oxygen use per day) 7. Plans to start or to change the pulmonary rehabilitation programme during the study period 8. Requires regular treatment with oral, parenteral, or depot corticosteroids 9. Serious, uncontrolled disease likely to interfere with the study (e.g. left ventricular failure, anaemia, renal or hepatic disease or serious psychological disorders) 10. Has, in the opinion of the investigator, evidence of alcohol, drug or solvent abuse

	11. Has a known or suspected hypersensitivity to β2-agonists, steroids, anticholinergic treatments or any components of the formulations
Interventions	**Inhaler device** 1. Salmeterol xinafoate / fluticasone propionate 50/250 µg Diskus 2. Tiotropium bromide 18 µg capsule **Allowed co-medications:** salbutamol as rescue
Outcomes	**Primary:** trough FEV1 after 12 weeks of treatment
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01762800, SCO116717

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was low and even between two groups (9.4% in tiotropium and 10.2 % in fluticasone propionate/salmeterol group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Covelli 2016

Methods	**Design:** randomised, double-blind, double-dummy, multicentre, parallel-group study **Duration:** 12 weeks **Location:** Canada, Czechia, Germany, Poland, Romania, USA
Participants	**Population** 1. Fluticasone furorate/vilanterol 100/25 µg (310) 2. Tiotropium 18 µg (313) **Baseline characteristics:** age 62.6 (SD 8.03), female:male 221:402 **Inclusion criteria**

	1. Signed and dated written informed consent 2. Men or women ≥ 40 years of age 3. Women must be post-menopausal or using a highly effective method for avoidance of pregnancy 4. Established clinical history of COPD by ATS/ERS definition 5. Post-albuterol spirometry criteria: FEV1/FVC ratio ≤ 0.70 and FEV1 ≥ 30 to ≤ 70% of predicted normal (NHANES 3) 6. Former or current smoker ≥ 10 pack-years 7. A history of diagnosed CVD or a prior cardiovascular event including any of the following: i) established (i.e. by clinical signs or imaging studies) coronary artery disease (CAD) ii) established (i.e. by clinical signs or imaging studies) peripheral vascular (i.e. arterial) disease (PVD)) iii) previous stroke iv) objectively confirmed TIA (i.e. transient neurological deficit documented by a health-care professional) v) previous MI (note: MI within 6 months prior to visit 1 is exclusionary) OR 1. Presence of one of the following cardiovascular risk factors (in addition to being a former/current smoker): i) current diagnosis of hypertension ii) current diagnosis of hypercholesterolaemia iii) diabetes mellitus treated with pharmacotherapy **Exclusion criteria** 1. Current diagnosis of asthma 2. Other respiratory disorders including α1-antitrypsin deficiency as the underlying cause of COPD, active TB, lung cancer, bronchiectasis (note: focal bronchiectasis is not exclusionary), sarcoidosis, pulmonary fibrosis (note: focal fibrotic pulmonary lesions are not exclusionary), pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases 3. Lung volume reduction surgery within previous 12 months 4. Clinically significant abnormalities not due to COPD by chest X-ray or CT scan 5. Hospitalised for poorly controlled COPD within 12 weeks of screening 6. Poorly controlled COPD 6 weeks prior to screening, defined as acute worsening of COPD that is managed by the participant with corticosteroids or antibiotics or that requires treatment prescribed by a physician 7. Lower respiratory infection requiring antibiotics 6 weeks prior to screening 8. A moderate or severe COPD exacerbation and/or a lower respiratory tract infection (including pneumonia) during the run-in period 9. An abnormal, clinically significant finding in any liver chemistry, biochemical, or haematology tests at screening (visit 1) or upon repeat prior to randomisation 10. An abnormal, clinically significant ECG finding at screening (visit 1) or upon repeat prior to randomisation 11. An abnormal, clinically significant Holter finding at screening (visit 1) or upon repeat prior to randomisation (subset of participants) 12. Historical or current evidence of clinically significant (in opinion of the investigator) and unstable disease such as cardiovascular (e.g. participants requiring

	ICD, pacemaker requiring a ventricular pace rate set at > 60 bpm, uncontrolled hypertension, New York Heart Association Class 4 (New York Heart Association,1994), known left ventricular ejection fraction < 30%), neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease), peptic ulcer disease, or haematological abnormalities 13. Carcinoma not in complete remission for at least 5 years 14. History of allergy or hypersensitivity to any of the study medications (e.g. anticholinergic/muscarinic receptor antagonist, beta2-agonist, corticosteroid) or components of the inhalation powder (e.g. lactose, magnesium stearate) or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the study physician contraindicates study participation or use of an inhaled anticholinergic. In addition, participants with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the participant's participation will also be excluded 15. Known/suspected history of alcohol or drug abuse in the last 2 years 16. Women who are pregnant or lactating or plan to become pregnant 17. Participants medically unable to withhold albuterol/salbutamol for 4 h prior to spirometry testing at each study visit 18. Use of certain medications such as bronchodilators and corticosteroids for the protocol-specific times prior to visit 1 (the investigator will discuss the specific medications) 19. LTOT or nocturnal oxygen therapy > 12 h/d 20. Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to screening or during the study 21. Failure to demonstrate adequate compliance defined as completion of the diary card (completed all diary entries on at least 4 of the last 7 consecutive days), the ability to withhold COPD medications and to keep clinic visit appointments 22. Non-compliance or inability to comply with study procedures or scheduled visits 23. History of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study 24. Affiliation with investigator site 25. Women who are pregnant or lactating or are planning on becoming pregnant during the study
Interventions	**Inhaler device** 1. Fluticasone furoate/vilanterol 100/25 μg inhalation powder 2. Tiotropium bromide 18 μg inhalation powder **Allowed co-medications:** rescue medication (albuterol) and mucolytics at a constant dosage
Outcomes	**Primary:** CFB trough in 24-h weighted mean FEV1 on treatment day 84
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01627327, HZC115805

Risk of bias

Bias	Authors' judgement	Support for judgement

Covelli 2016 (*Continued*)

Random sequence generation (selection bias)	Low risk	A central randomisation schedule was generated using a validated computerised system (RandAll; GSK) and communicated with a validated computerised voice-response system, the Registration and Medication Ordering System (RAMOS; GSK)
Allocation concealment (selection bias)	Low risk	A central randomisation schedule was generated using a validated computerised system (RandAll; GSK) and communicated with a validated computerised voice-response system, the Registration and Medication Ordering System (RAMOS; GSK)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator and treating physician were kept blinded unless a medical emergency or a serious adverse medical condition arose
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was uneven between 2 groups (fluticasone furorate/vilanterol 6.1% and tiotropium 12.4%)
Selective reporting (reporting bias)	Low risk	Outcomes stated on preregistered protocol were well reported

D'Urzo 2014

Methods	**Design:** phase 3, randomised, double-blind, placebo-controlled study **Duration:** 24 weeks **Location:** Australia, Canada, New Zealand, USA
Participants	**Population** 1. Aclidinium/formoterol 400/12 µg (325) 2. Aclidinium 400 µg (337) 3. Formoterol 12 µg (332) **Baseline characteristics:** age 63.9 (SD 8.9) female:male 782:887 **Inclusion criteria** Patients aged ≥40 years were eligible if they were current or former smokers (≥10 pack-years) and diagnosed with stable, moderate to severe expiratory airflow obstruction according to GOLD guidelines (postbronchodilator FEV1/FVC <70% and FEV1 ≥30% and <80% predicted) **Exclusion criteria** COPD exacerbation or respiratory tract infection ≤6 weeks (≤3 months if hospitalized for exacerbation) before screening; clinically significant respiratory conditions (in-

	cluding asthma); clinically significant cardiovascular conditions including MI within the previous 6 months; unstable angina; and, unstable arrhythmia that required changes in pharmacological therapy or other intervention within the previous 6 months
Interventions	1. Inhaled aclidinium/formoterol 400/12 μg, twice daily 2. Inhaled aclidinium 400 μg, twice daily 3. Inhaled formoterol 12 μg, twice daily 4. Inhaled dose-matched placebo, twice daily **Inhaler device:** multidose DPI **Allowed co-medications:** albuterol/salbutamol as rescue, theophylline, ICS, OCS or parenteral corticosteroids ($\leq$ 10 mg/d or 20 mg every other day of prednisone) were allowed if treatment was stable $\geq$ 4 weeks prior to screening
Outcomes	**Primary:** CFB in 1-h morning post-dose FEV1, CFB in morning trough FEV1
Notes	**Funding:** AstraZeneca **Identifiers:** NCT01437397, LAC-MD-31

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cardiac AEs were evaluated by an adjudication committee of independent cardiologists who were not participating in the study and were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was relatively high but even among the arms of interest (19.5% in aclidinium/formoterol 400/12µg, 21.2% in aclidinium 400µg, and 20.4% in formoterol 12µg)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

D'Urzo 2017

Methods	**Design:** phase 3, long-term, randomised, double-blind, extension study **Duration:** 28-52 weeks **Location:** Australia, Canada, New Zealand, USA
Participants	**Population** 1. Aclidinium/formoterol 400/12 µg (338) 2. Aclidinium 400 µg (340) 3. Formoterol 12 µg (339) **Baseline characteristics:** age 63.2 (SD 8.8), female:male 435:483 **Inclusion criteria** 1. Completion of the treatment phase of the lead-in study, LAC-MD-31 2. Written informed consent obtained from the participant before the initiation of any study specific procedures 3. No medical contraindication as judged by the primary investigator 4. Compliance with LAC-MD-31 study procedures and investigational product dosing. **Exclusion criteria** 1. No specific exclusion criteria
Interventions	1. Inhaled aclidinium/formoterol 400/12 μg, twice daily 2. Inhaled aclidinium 400 μg, twice daily 3. Inhaled formoterol 12 μg, twice daily 4. Inhaled dose-matched placebo, twice daily **Inhaler device:** **Allowed co-medications:** theophylline, ICS, oral or parenteral corticosteroids (10 mg/d or 20 mg every other day prednisone) were allowed if treatment was stable within 4 weeks of the lead-in trial start. Albuterol (108 µg/puff) or salbutamol (100 µg/puff) were the only rescue medications permitted during the study
Outcomes	**Primary:** percentage of participants to experience any treatment-emergent AE
Notes	**Funding:** AstraZeneca **Identifiers:** NCT01572792, LAC-MD-36

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Unclear risk	Not described

D'Urzo 2017 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was relatively high but even among the arms of interest (15.8% in aclidinium/formoterol 400/12µg, 14.9% in aclidinium 400µg, and 16.7% in formoterol 12µg)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Dahl 2010

Methods	**Design**: randomised double-blind double-dummy parallel-group study **Duration**: 12 months (+ 2-week run-in period) **Location**: Denmark, Germany, Russia, UK, USA (unclear how many centres)
Participants	**Population:** 1732 participants were randomised to 1. formoterol (435), 2. two doses of indacaterol (437 and 428) 3. placebo (432) **Baseline characteristics** Mean age (years): formoterol 64, indacaterol (300 μg) 64, indacaterol (600 μg) 63, placebo 63 % male: formoterol 80.2, indacaterol (300 μg) 80.3, indacaterol (600 μg) 76.9, placebo 81.5 % FEV1 predicted: formoterol 52.5, indacaterol 300 μg 51.5, indacaterol 600 μg 50.8, placebo 52.0 Pack-years: formoterol 40, indacaterol 300 μg 40, indacaterol 600 μg 40, placebo 43 **Inclusion criteria**: men and women aged $\geq$ 40; clinical diagnosis of moderate-severe COPD; history of at least 20 pack-years **Exclusion criteria**: history of asthma; current respiratory tract infection or hospitalisation for COPD exacerbation within the previous 6 weeks
Interventions	1. Formoterol 12 μg twice daily (LABA) 2. Indacaterol 300 μg once daily (LABA) 3. Indacaterol 600 μg once daily (LABA) 4. Placebo (placebo) **Inhaler device**: dry powder turbuhaler and single dose DPI **Allowed co-medications:** fixed-dose combinations of ICS + LABA were replaced by monotherapy ICS at an equivalent dose and regimen + salbutamol as needed. Participants receiving ICS monotherapy continued treatment at a stable dose throughout the study. OCS were not allowed, or a change in ICS was noted during the previous month
Outcomes	SGRQ, COPD exacerbations, trough FEV1 and PEF, dyspnoea (baseline and transition scores), diary card data, 6MWD, ECG, vital signs and haematology

Dahl 2010 *(Continued)*

Notes	**Funding**: Novartis **Identifier(s)**: NCT00393458

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised to treatment (1:1:1:1) with stratification for smoking status (current/ex-smoker) using an automated interactive system
Allocation concealment (selection bias)	Low risk	Using an automated interactive system (concealment assumed by automatisation)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Protocol states double-blind for participant, caregiver, investigator and outcomes assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy results are presented for the modified ITT population including all randomised participants who received at least 1 dose of study drug. Withdrawal relatively high (indacaterol 300 22.7%; formoterol 25.7%) but reasons for dropout were similar across the active comparators
Selective reporting (reporting bias)	Low risk	All stated and expected outcomes reported in detail

Decramer 2013

Methods	**Design: p**hase 3b multicentre, 52-week treatment, randomised, blinded, double-dummy, parallel-group efficacy study **Duration:** 52 weeks **Location:** Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Colombia, Costa Rica, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, India, Israel, Italy, Latvia, Lithuania, Mexico, Netherlands, Peru, Philippines, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, UK, Venezuela
Participants	**Population** 1. Indacaterol 150 µg (1721) 2. Tiotropium 18 µg (1718)

	Baseline characteristics: age 64.0 (range 40-91) female:male 782:2657 **Inclusion criteria** 1. Men and women aged ≥ 40 years, 2. Signed informed consent form prior to initiation of any study-related procedure 3. Diagnosed with COPD at age ≥ 40 with a current diagnosis of severe COPD and including: smoking history of at least 10 pack-years, both current and ex-smokers are eligible. 4. A documented history of at least 1 moderate or severe exacerbation in the previous 12 months **Exclusion criteria** 1. Systemic corticosteroids and/or antibiotics for a COPD exacerbation in the 6 weeks prior to screening or during the run-in period 2. Respiratory tract infection within 6 weeks prior to screening 3. Concomitant pulmonary disease 4. History of asthma 5. Diabetes type 1 or uncontrolled diabetes type 2 6. Lung cancer or a history of lung cancer 7. History of certain cardiovascular comorbid condition
Interventions	**Inhaler device** 1. Indacaterol 150 µg once daily delivered via DPI 2. Tiotropium 18 µg once daily delivered via HandiHaler **Allowed co-medications:** as-needed albuterol or salbutamol, ICS
Outcomes	**Primary:** trough FEV1
Notes	**Funding:** Novartis **Identifiers:** NCT00845728, QAB149B2348

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence was computer-generated by an interactive voice-response system (IVRS; Oracle America Inc, Redwood City, CA, USA)
Allocation concealment (selection bias)	Low risk	Randomisation sequence was computer-generated by an interactive voice-response system (IVRS; Oracle America Inc, Redwood City, CA, USA)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy trial

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was relatively high but even among the arms of interest (22.4% in indacaterol, 19.9% in tiotropium)
Selective reporting (reporting bias)	Low risk	All stated and expected outcomes reported in detail

Decramer 2014a

Methods	**Design: p**hase 3 multicentre, randomised, double-blind, double-dummy, parallel-group study **Duration:** 24 weeks **Location:** France, Germany, Italy, Mexico, Peru, Poland, Romania, Russian Federation, Ukraine, USA
Participants	**Population** 1. Umeclidinium/vilanterol 62.5/25 µg (212) 2. Tiotropium 18 µg (208) **Baseline characteristics:** age 62.9 (SD 9), female:male 261:582 **Inclusion criteria** 1. Outpatient 2. Signed and dated written informed consent 3. $\geq$ 40 years 4. Male and female participants 5. COPD diagnosis 6. $\geq$ 10 pack-year smoking history 7. Post-albuterol/salbutamol FEV1/FVC ratio of < 0.70 and post-albuterol/salbutamol FEV1 $\leq$ to 70% predicted normal values 8. score of $\geq$ 2 on the mMRC **Exclusion criteria** 1. Current diagnosis of asthma 2. Respiratory disorders other than COPD 3. Other diseases/abnormalities that are uncontrolled including cancer not in remission for at least 5 years 4. Hospitalisation for COPD or pneumonia within 12 weeks prior to visit 1 5. Lung volume reduction surgery within 12 months prior to visit 1 6. Abnormal and clinically significant ECG at visit 1 7. Significantly abnormal finding from laboratory tests at visit 1 8. Use of depot corticosteroids within 12 weeks of visit 1 9. Use of oral or parenteral corticosteroids, antibiotics for lower respiratory tract infection, or cytochrome P450 3A4 inhibitors, within 6 weeks of visit 1 10. Use of LABA/ICS product if LABA/ICS therapy is discontinued within 30 days of visit 1 11. Use of ICS at a dose of > 1000 μg/day of fluticasone propionate or equivalent

	within 30 days of visit 1 12. Initiation or discontinuation of ICS within 30 days of visit 1 13. Use of tiotropium or roflumilast within 14 days of visit 1 14. Use of theophyllines, oral leukotriene inhibitors, long-acting oral beta-agonists, or inhaled LABA within 48 h of visit 1 15. Oral SABAs within 12 h of visit 1 16. Use of LABA/ICS combination products only if discontinuing LABA therapy and switching to ICS monotherapy within 48 h of visit 1 for the LABA component 17. Use of sodium cromoglycate or nedocromil sodium within 24 h of visit 1 18. Use of inhaled SABAs, inhaled short-acting anticholinergics, or inhaled short-acting anticholinergic/SABA combination products within 4 h of visit 1 19. LTOT prescribed for > 12 h/d 20. Regular use of nebulised short-acting bronchodilators
Interventions	1. GSK573719/GW642444 (umeclidinium/vilanterol) 62.5/25 μg 2. GW642444 (vilanterol trifenatate) 25 μg 3. Tiotropium bromide 18 μg **Inhaler device:** ELLIPTA DPI and the HandiHaler DPI **Allowed co-medications**: albuterol as needed, ICS
Outcomes	CFB trough FEV1 on day 169 (week 24)
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01316900, DB2113360

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Allocation concealment (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Investigator and treating physician were kept blinded unless a medical emergency or

Decramer 2014a (*Continued)*

All outcomes		a serious adverse medical condition arose
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was relatively high but even among the arms of interest (14.6% in umeclidinium/vilanterol 62.5/25, 14.9% in tiotropium group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Decramer 2014b

Methods	**Design:** a phase 3 multicentre, randomised, double-blind, double-dummy, parallel-group study **Duration:** 24 weeks **Location:** Argentina, Australia, Canada, Chile, Germany, Republic of Korea, Mexico, Romania, South Africa, USA
Participants	**Population** 1. Umeclidinium/vilanterol 62.5/25 μg (217) 2. Tiotropium 18 μg (215) **Baseline characteristics:** age 64.6 (SD 8.44) female:male 280:589 **Inclusion criteria** 1. Outpatient 2. Signed and dated written informed consent 3. $\geq$ 40 years old 4. Male and female participants 5. COPD diagnosis 6. $\geq$ 10 pack-year smoking history 7. Post-albuterol/salbutamol FEV1/FVC ratio of < 0.70 and post-albuterol/salbutamol FEV1 of $\leq$ 70% predicted normal values 8. Score of $\geq$ 2 on the mMRC Dyspnea Scale **Exclusion criteria** 1. Current diagnosis of asthma 2. Respiratory disorders other than COPD 3. Other diseases/abnormalities that are uncontrolled including cancer not in remission for at least 5 years 4. Hospitalisation for COPD or pneumonia within 12 weeks prior to visit 1 5. Lung volume reduction surgery within 12 months prior to visit 1 6. Abnormal and clinically significant ECG at visit 1 7. Significantly abnormal finding from laboratory tests at visit 1 8. Use of depot corticosteroids within 12 weeks of visit 1 9. Use of oral or parenteral corticosteroids, antibiotics for lower respiratory tract infection, or cytochrome P450 3A4 inhibitors, within 6 weeks of visit 1 10. Use of LABA/ICS product if LABA/ICS therapy is discontinued within 30 days of visit 1 11. Use of ICS at a dose of > 1000 μg/day of fluticasone propionate or equivalent within 30 days of visit 1

	12. Initiation or discontinuation of ICS within 30 days of visit 1 13. Use of tiotropium or roflumilast within 14 days of visit 1 14. Use of theophyllines, oral leukotriene inhibitors, long-acting oral beta-agonists, or inhaled LABA within 48 h of visit 1 15. Oral SABAs within 12 h of visit 1 16. Use of LABA/ICS combination products only if discontinuing LABA therapy and switching to ICS monotherapy within 48 h of visit 1 for the LABA component 17. Use of sodium cromoglycate or nedocromil sodium within 24 h of visit 1 18. Use of inhaled SABAs, inhaled short-acting anticholinergics, or inhaled short-acting anticholinergic/SABA combination products within 4 h of visit 1 19. LTOT prescribed for > 12 h/d 20. Regular use of nebulised short-acting bronchodilators
Interventions	1. GSK573719/GW642444 (umeclidinium/vilanterol) 62.5/25 μg 2. GW642444 (vilanterol trifenatate) 25 μg 3. tiotropium bromide 18 μg **Inhaler device:** ELLIPTA DPI and the HandiHaler DPI **Allowed co-medications:** albuterol as needed, ICS
Outcomes	**Primary:** CFB in clinic visit trough FEV1 at day 169
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01316913, DB2113374

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Allocation concealment (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator and treating physician were kept blinded unless a medical emergency or a serious adverse medical condition arose

Decramer 2014b (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was relatively high and uneven among the arms of interest (24.9% in umeclidinium/vilanterol 62.5/25, 18.1% in tiotropium group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Donohue 2010

Methods	**Design**: this study was performed in 2 stages in an adaptive seamless design 1. Participants randomised to receive indacaterol 75, 150, 300 μg, or 600 μg once daily, formoterol 12 μg twice daily, or placebo, all double-blind, or open-label tiotropium 18 μg once daily. An independent committee used predefined efficacy criteria to select 2 indacaterol doses based on 2-week efficacy and safety data. These were 150 and 300 μg . 2. The 4 treatment groups were the 2 selected doses of indacaterol, tiotropium, and placebo. Treatment continued to 26 weeks, with additional participants recruited and randomised **Duration**: 26 weeks (+ 2 week run-in) **Location**: 345 centres in 12 countries
Participants	**Population**: 1683 participants were randomised to 1. indacaterol at 2 doses (416 and 416) 2. open-label tiotropium (415) 3. placebo (418) - not included in this review **Baseline characteristics** Age (mean years): indacaterol (150 μg) 63.4, indacaterol (300 μg) 63.3, tiotropium 64.0, placebo 63.6 % male: indacaterol (150 μg) 62.3, indacaterol (300 μg) 63.2, tiotropium 64.8, placebo 61.0 % FEV1 predicted: indacaterol 150 μg 56.1, indacaterol 300 μg 56.3, tiotropium 53.9, placebo 56.1 Pack-years (mean): indacaterol 150 μg 48.3, indacaterol 300 μg 50.8, tiotropium 50.0, placebo 49.7 **Inclusion criteria**: Male and female adults aged 40 years, who have signed an informed consent form prior to initiation of any study-related procedure. Co-operative outpatients with a diagnosis of COPD (moderate-severe as classified by GOLD 2005 criteria) and smoking history of at least 20 pack-years. Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value. Post-bronchodilator FEV1/FVC < 70% (Post refers to within 30 min of inhalation of 400 μg of salbutamol) **Exclusion criteria**: lactating women; hospitalised for a COPD exacerbation in the 6 weeks prior to visit 1 or during the run-in period; requiring LTOT (> 15 h/d); respiratory tract infection 6 weeks prior to visit 1; concomitant pulmonary disease, pulmonary TB, or clinically significant bronchiectasis; history of asthma; type 1 or uncontrolled type 2 diabetes; contraindications for tiotropium; clinically relevant laboratory abnormalities or a clinically significant abnormality; active cancer or a history of cancer with < 5 years disease-free survival time; history of long QT syndrome or whose QTc interval

	is prolonged; hypersensitivity to any of the study drugs or drugs with similar chemical structures; treatment with the investigational drug (with further criteria); live attenuated vaccinations within 30 days prior to visit 1, or during run-in period; known history of non compliance to medication; unable to satisfactorily use a DPI device or perform spirometry measurements
Interventions	1. Indacaterol 150 μg once daily (LABA) 2. Indacaterol 300 μg once daily (LABA) 3. Tiotropium 18 μg once daily (LAMA) - open-label 4. Placebo (placebo) **Inhaler device**: 1, 2, and 4 via single-dose DPI, open-label tiotropium via HandiHaler **Allowed co-medications**: participants could continue ICS monotherapy if stable for 1 month before screening; dose and regimen were to remain stable throughout the study. Before the start of the run-in period, treatment with anticholinergic bronchodilators or with 2-agonists was discontinued with appropriate washout, and participants receiving fixed-combination 2-agonist/ICS were switched to ICS monotherapy at an equivalent dose. All participants were supplied with albuterol for use as needed
Outcomes	The primary efficacy outcome was trough FEV1 at 12 weeks. Additional analyses (not adjusted for multiplicity) included TDI, health status SGRQ, and exacerbations. Serum potassium, blood glucose, and QTc interval were measured
Notes	**Funding**: Novartis **Identifier(s)**: NCT00463567 and CQAB149B2335S

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using an automated interactive voice-response system, and was stratified by smoking status (current or ex-smoker)
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding procedures were sound, but tiotropium was delivered open-label, which introduced bias for these comparisons. On completion of stage 1, the independent dose selection committee had access to unblinded data. The only information communicated with the sponsor and investigators was the 2 selected indacaterol doses, and personnel involved in the continuing clinical study remained blinded for the remainder of the study. The blinding of indacaterol and placebo continued until the

Donohue 2010 *(Continued)*

		study database was locked at the end of stage 2
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding procedures were sound, but tiotropium was delivered open-label, which introduced bias for these comparisons. Double-blind (participant, caregiver, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy was evaluated for the ITT population, comprising all randomised participants who received at least 1 dose of study drug. Dropout was variable and generally high across groups (ranging from 18%-31%). 98.9% were included in the analysis
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports and clinicaltrials.gov

Donohue 2013

Methods	**Design:** a phase 3 multicentre, randomised, double-blind, placebo-controlled, parallel-group study **Duration:** 24 weeks **Location:** Bulgaria, Canada, Chile, Czechia, Greece, Japan, Mexico, Poland, Russian Federation, South Africa, Spain, Thailand, USA
Participants	**Population** 1. Umeclidinium/vilanterol 62.5/25 (413) 2. Umeclidinium 62.5 (418) **Baseline characteristics:** age 63.1 (SD 8.86) female:male 449: 1083 **Inclusion criteria** 1. Diagnosis of COPD 2. $\geq$ 10 pack-year history of cigarette smoking 3. Post-bronchodilator FEV1/FVC < 0.7 4. Predicted FEV1 of $\leq$ 70% of normal 5. mMRC dyspnoea score of $\geq$ 2 **Exclusion criteria** 1. Women who are pregnant, lactating, or planning to become pregnant 2. Respiratory disorders other than COPD, including a current diagnosis of asthma 3. Clinically significant non-respiratory diseases or abnormalities that are not adequately controlled 4. Significant allergy or hypersensitivity to anticholinergics, beta-agonist, or the excipients of magnesium stearate or lactose used in the inhaler delivery device 5. Hospitalisation for COPD or pneumonia within 12 weeks prior to screening 6. Lung volume reduction surgery within 12 weeks prior to screening 7. Abnormal and clinically significant ECG findings at screening

	8. Clinically significant laboratory findings at screening 9. Use of systemic corticosteroids, antibiotics for respiratory tract infections, strong cytochrome P450 3A4 inhibitors, high-dose inhaled steroids (> 1000 μg fluticasone propionate or equivalent), PDE4 inhibitors, tiotropium, oral beta2-agoinists, short- and long-acting inhaled beta2-agonists, ipratropium, inhaled sodium cromoglycate or nedocromil sodium, or investigational medicines for defined time periods prior to the screening visit 10. Use of LTOT ($\geq$ 12 h/d) 11. Regular use of nebulised treatment with short-acting bronchodilators 12. Participation in the acute phase of a pulmonary rehabilitation programme 13. A known or suspected history of alcohol or drug abuse 14. Affiliation with the investigational site 15. Previous use of GSK573719 or GW642444 alone or in combination, including the combination of fluticasone furoate and GW64244
Interventions	1. GSK573719/GW64244 (umeclidinium/vilanterol) 62.5/25 μg 2. GSK573719 (umeclidinium) 62.5 μg **Inhaler device:** DPI **Allowed co-medications:** salbutamol (albuterol) as rescue medication was allowed. ICS were allowed at a stable dose of 1000 μg/day of fluticasone propionate or equivalent
Outcomes	**Primary:** CFB in trough FEV1 on day 169 (week 24)
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01313650, DB2113373

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A central randomisation schedule was generated using a validated computerised system (RandAll). Participants were randomised using an automated, interactive telephone-based system that registered and randomised medication assignment
Allocation concealment (selection bias)	Low risk	A central randomisation schedule was generated using a validated computerised system (RandAll). Participants were randomised using an automated, interactive telephone-based system that registered and randomised medication assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Donohue 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator and treating physician were kept blinded unless a medical emergency or a serious adverse medical condition arose
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was relatively high but even between the arms of interest (22.5% in umeclidinium 62.5µg , 19.6 % in umeclidinium/vilanterol 62.5/25µg group)
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports and clinicaltrials.gov

Donohue 2015a

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial **Duration:** 7 countries (USA and European countries), 63 centres **Location:** 12 weeks
Participants	**Population** 1. Umeclidinium/vilanterol (353) 2. Fluticasone propionate/salmeterol (353) **Baseline characteristics** Age: 62.8 (SD 9.0) years Male/female: 497/209 % pred FEV1: 49.4% (SD 10.9) **Inclusion criteria:** % pred FEV1 30% -70%, mMRC $\geq$ 2, no recent exacerbation **Exclusion criteria:** pregnancy/breast feeding, asthma, other respiratory disorders, clinically significant comorbidities, hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist, corticosteroid, history of COPD exacerbation: documented history of at least one COPD exacerbation in the 12 months prior to visit 1, recent lung resection < 12 months, LTOT > 12 h/d, drug or alcohol abuse
Interventions	1. Umeclidinium/vilanterol (62.5/25 μg) once daily (LAMA/LABA) 2. Salmeterol/fluticasone (50/250 μg) twice daily (LABA/ICS) 3. Placebo **Inhaler device:** 1. Dry white powder delivered via DPI (umeclidinium/vilanterol) 2. Dry white powder delivered via Accuhaler/Diskus (fluticasone propionate/ salmeterol) **Allowed co-medications:** SABAs as rescue
Outcomes	**Primary:** CFB in 24-h weighted-mean serial FEV1 on day 84
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01817764, DB2114930

Donohue 2015a (*Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK)
Allocation concealment (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The site personnel involved in making study assessment were aware of a participant's treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rate was low and even between active comparators, 9.6% in umeclidinium/vilanterol arm and 10.8% in salmeterol/fluticasone arm
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

Donohue 2015b

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled **Duration:** 12 weeks **Location:** 7 countries (USA, Russia and European countries), 71 centres
Participants	**Population** 1. Umeclidinium/vilanterol (349) 2. Fluticasone propionate/salmeterol (348) **Baseline characteristics** Age: 63.6 (SD 8.9) years Male/female: 528/169 % pred FEV1: 49.5% (SD 10.9) **Inclusion criteria:** % pred FEV1 30%-70%, mMRC $\geq$ 2, no recent exacerbation **Exclusion criteria:** pregnancy/breast feeding, asthma, other respiratory disorders, clinically significant comorbidities, hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist, corticosteroid, history of COPD exacerbation: documented history of at least one COPD exacerbation in the 12 months prior to visit 1, recent lung resection < 12 months, LTOT > 12 h/d, drug or alcohol abuse

Interventions	1. Umeclidinium/vilanterol (62.5/25 μg) (LAMA/LABA) 2. Salmeterol/fluticasone (50/250 μg) twice daily (LABA/ICS) **Inhaler device:** 1. Dry white powder delivered via DPI (umeclidinium/vilanterol) 2. Dry white powder delivered via Accuhaler/Diskus (fluticasone propionate/salmeterol) **Allowed co-medications:** SABA as rescue
Outcomes	**Primary:** CFB in 24-h weighted-mean serial FEV1 on treatment day 84
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01879410, DB2114951

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK)
Allocation concealment (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The site personnel involved in making study assessment were aware of a participant's treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rate was low and relatively even between active comparators, 6.9% in umeclidinium/vilanterol arm and 10.9% in salmeterol/fluticasone arm
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

Donohue 2016a

Methods	**Design:** phase 3, randomised, double-blind, parallel-group, active-control study **Duration:** 52 weeks **Location:** 127 centres in the USA
Participants	**Population** 1. Aclidinium/formoterol 400/12 μg (392) 2. Formoterol 12 μg (198) **Baseline characteristics:** age 64.2 (SD 9.4) female:male 265:325 **Inclusion criteria** 1. Current or former cigarette smokers with a cigarette smoking history of at least 10 pack-years 2. A diagnosis of stable moderate-severe COPD and stable airway obstruction as defined by the GOLD criteria and stable airway obstruction. **Exclusion criteria** • Hospitalised for an acute COPD exacerbation within 3 months prior to visit 1 • Any respiratory tract infection (including the upper respiratory tract) or COPD exacerbation in the 6 weeks before visit 1 • Any clinically significant respiratory conditions other than COPD • Clinical history that suggests asthma as opposed to COPD • Chronic use of oxygen therapy $\geq$ 15 h/d • Clinically significant cardiovascular conditions • Uncontrolled infection that may place the participant at risk resulting from HIV, active hepatitis and/or with diagnosed active TB • History of hypersensitivity reaction to inhaled anticholinergics • Stage 2 hypertension, defined as systolic pressure of $\geq$ 160, and/or diastolic pressure of $\geq$ 100 • Current diagnosis of cancer other than basal or squamous cell skin cancer
Interventions	1. Aclidinium bromide/formoterol fumarate 2. Formoterol fumarate **Inhaler device:** multidose DPI **Allowed co-medications:** as-needed albuterol, ICS and OCS or parenteral corticosteroids at doses 10 mg/d, theophylline and H1-antihistamine were permitted
Outcomes	**Primary:** % participants to experience at least 1 treatment-emergent AE
Notes	**Funding:** AstraZeneca **Identifiers:** NCT01437540, LAC-MD-32

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out by assigning participant identification numbers via an interactive web-response system
Allocation concealment (selection bias)	Low risk	Randomisation was carried out by assigning participant identification numbers via

Donohue 2016a (*Continued*)

		an interactive web-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Major cardiac AEs were evaluated and classified according to the criteria prespecified by 3 blinded independent expert cardiologists not participating in the study
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was relatively high (32.4% in aclidinium/formoterol and 32.8% in formoterol) and breakdown for dropouts was uneven. ITT population was used without description of imputation
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports

Dransfield 2014

Methods	**Design:** randomised, multicentre, double-blind, double-dummy, parallel-group, comparative studies **Duration:** 12 weeks **Location** Study 1**:** 51 centres in 6 countries (Czech Republic, Germany, Poland, Romania, Russia, USA) Study 2: 48 centres in 5 countries (Italy, South Africa, Spain, Ukraine, USA) Study 3: 68 centres in 5 countries (Germany, Romania, Russia, Ukraine, USA)
Participants	**Population** 1. Fluticasone propionate/salmeterol 250/50 μg (927) 2. Fluticasone furorate/vilanterol 100/25 μg (931) **Baseline characteristics:** age 61 (SD 9), female:male 582:1276 **Inclusion criteria** 1. Signed and dated written informed consent 2. Men or women $\geq$ 40 years of age 3. Established clinical history of COPD by ATS/ERS definition 4. Women eligible to enter and participate if of non-childbearing potential, or if of child bearing potential, had a negative serum pregnancy test at screening, and agreed to one of the acceptable contraceptive methods listed in protocol, used consistently and correctly 5. Former or current smoker > 10 pack-years 6. Post-albuterol spirometry criteria: FEV1/FVC ratio $\leq$ 0.70 and FEV1 $\leq$ 70% of predicted normal (NHANES 3)

	Exclusion criteria 1. Current diagnosis of asthma 2. Other respiratory disorders including active TB, α1-antitrypsin deficiency, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases 3. Lung volume reduction surgery within previous 12 months 4. Clinically significant abnormalities not due to COPD by chest X-ray 5. Hospitalised for poorly controlled COPD within 12 weeks of screening 6. Poorly controlled COPD 6 weeks prior to screening, defined as acute worsening of COPD that is managed by the participant with corticosteroids or antibiotics or that requires treatment prescribed by a physician 7. Lower respiratory infection requiring antibiotics 6 weeks prior to screening 8. Uncontrolled or clinically significant (in opinion of PI) cardiovascular, hypertension, neurological, psychiatric, renal, hepatic, immunological, endocrine, peptic ulcer disease, or haematological abnormalities 9. Carcinoma not in complete remission for at least 5 years 10. History of hypersensitivity to study medications (e.g. beta-agonists, corticosteroid) or components of inhalation powder (e.g. lactose, magnesium stearate) 11. History of severe milk protein allergy that, in opinion of study physician, contraindicates participation 12. Known/suspected history of alcohol or drug abuse in the last 2 years 13. Women who are pregnant or lactating or plan to become pregnant 14. Medically unable to withhold albuterol and/or ipratropium 4 h prior to spirometry testing at each study visit 15. Use of certain medications such as bronchodilators and corticosteroids for the protocol-specific times prior to visit 1 (the PI will discuss the specific medications) 16. LTOT or nocturnal oxygen therapy > 12 h/d 17. Participation in the acute phase of a pulmonary rehabilitation programme within 4 weeks prior to screening or during the study 18. Non-compliance or inability to comply with study procedures or scheduled visits
Interventions	**Inhaler device** 1. Fluticasone furoate/vilanterol: inhalation powder 100/25 μg 2. Fluticasone propionate/salmeterol: inhalation powder 250/50 μg **Allowed co-medications:** as-needed albuterol**,** ipratropium and mucolytics
Outcomes	**Primary:** CFB trough in 24-h weighted mean FEV1 on treatment day 84
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01323621; NCT01323634;NCT01706328, HZC112352; HZC113109; RLV116974

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System

Dransfield 2014 (*Continued*)

		(RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Allocation concealment (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator and treating physician were blinded until an emergency arose
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout low in both included groups (9.3% in fluticasone furorate/vilanterol and 9.1% in fluticasone propionate/salmeterol group)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Feldman 2016

Methods	**Design:** multicentre, randomised, blinded, double-dummy, parallel-group study **Duration:** 12 weeks **Location:** Argentina, Canada, Chile, Denmark, France, Germany, Italy, Republic of Korea, Romania, Russian Federation, South Africa, Ukraine, USA
Participants	**Population** 1. Umeclidinium 62.5 μg (509) 2. Tiotropium 18 μg (508) **Baseline characteristics:** age 64.2 (SD 8.2), female:male 282:735 **Inclusion criteria** 1. Outpatients 2. Signed and dated written informed consent prior to study participation required. 3. $\geq$ 40 years of age at visit 1 4. Male and female participants eligible to participate in the study. **Exclusion criteria** Pregnancy, a current diagnosis of asthma or other significant respiratory disorder or other condition that may affect respiratory function (e.g., unstable or life-threatening cardiac disease, a neurological condition), lung volume reduction surgery, or hospitalization for COPD/pneumonia within 12 weeks prior to Visit 1. Patients were also excluded for the use of long-term oxygen therapy (prescribed for .12 hours per day) and use of COPD

	maintenance medications other than study medication, with the exception of ICSs
Interventions	**Inhaler device:** 1. Umeclidinium: DPI 2. Tiotropium: Handihaler **Allowed co-medications:** albuterol/salbutamol for use as a rescue medication, ICSs
Outcomes	**Primary:** CFB in trough FEV1 on day 85
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT02207829, GSK201316

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Allocation concealment (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator and treating physician were kept blinded unless a medical emergency or a serious adverse medical condition arose
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was low and even between two groups.(8.3% in umeclidinium 6.7% in tiotropium group)
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports

Ferguson 2008

Methods	**Design**: randomised, double-blind, parallel-group study **Duration**: 12 months (+ 4-week run-in) **Location**: 94 research sites in the USA and Canada
Participants	**Population:** 782 people were randomised to 1. salmeterol (388) 2. fluticasone/salmeterol combination (394) **Baseline characteristics** Age (mean years): salmeterol 65.0, fluticasone/salmeterol 64.9 % male: salmeterol 52, fluticasone/salmeterol 58 % FEV1 predicted: salmeterol 32.8, fluticasone/salmeterol 32.8 Pack-years (mean): salmeterol 54.4, fluticasone/salmeterol 58.5 **Inclusion criteria**: $\geq$ 40 years of age with a diagnosis of COPD; a cigarette smoking history of $\geq$ 10 pack-years, a pre-albuterol FEV1/FVC $\leq$ 0.70, a FEV1 $\leq$ 50% of predicted normal and a history of $\geq$ 1 exacerbations of COPD in the year prior to the study that required treatment with OCS, antibiotics, or hospitalisation **Exclusion criteria**: diagnosis of asthma, a significant lung disease other than COPD, a clinically significant and uncontrolled medical disorder including but not limited to cardiovascular, endocrine or metabolic, neurological, psychiatric, hepatic, renal, gastric, and neuromuscular diseases, or had a COPD exacerbation that was not resolved at screening
Interventions	1. Salmeterol 50 μg twice daily (LABA) 2. Salmeterol/fluticasone 50/250 μg twice daily (LABA/ICS) **Inhaler device:** Diskus DPI **Allowed co-medications:** as-needed albuterol was provided for use throughout the study. The use of concurrent inhaled long-acting bronchodilators (beta2-agonist and anticholinergic), ipratropium/albuterol combination products, oral beta-agonists, ICSs, and theophylline preparations were not allowed during the treatment period. OCS and antibiotics were allowed for the acute treatment of COPD exacerbations
Outcomes	COPD exacerbations, pre-dose FEV1, diary records of dyspnoea, night-time awakenings due to COPD, and use of supplemental albuterol
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT00144911, GSK SCO40043

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centre-based randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind (presumed participants and personnel/investigators)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout high and fairly even (30% vs 38%). More participants in salmeterol arm compared with salmeterol/fluticasone group were discontinued from the study due to lack of efficacy and exacerbation
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports and clinicaltrials.gov

Ferguson 2016

Methods	**Design:** multicentre, randomised, double-blind, parallel-group study **Duration:** 52 weeks **Location:** 88 centres in 6 countries: Bulgaria (5), Finland (4), Hungary (10), Romania (10), Spain (8), USA (51)
Participants	**Population:** 615 participants randomised to 1. indacaterol/glycopyrrolate 27.5/15.6 μg twice daily (204) 2. indacaterol/glycopyrrolate 27.5/31.2 μg twice daily (204) - not included in this review 3. indacaterol 75 μg daily (207) **Baseline characteristics** Age (mean): indacaterol/glycopyrrolate 27.5/15.6 (64.7), indacaterol/glycopyrrolate 27.5/31.2 (63.9), indacaterol 75 (62.8) Male (%): indacaterol/glycopyrrolate 27.5/15.6 (64.2), indacaterol/glycopyrrolate27.5/31.2 (60.3), indacaterol 75 (72) FEV1 L (pre BD): indacaterol/glycopyrrolate 27.5/15.6 (1.254), indacaterol/glycopyrrolate 27.5/31.2 (1.232), indacaterol 75 (1.278) Current smokers (%): indacaterol/glycopyrrolate 27.5/15.6 (49.5), indacaterol/glycopyrrolate 27.5/31.2 (51.5), indacaterol 75 (51.7) **Inclusion criteria** Male and female, aged $\geq$ 40 years with stable COPD according to GOLD 2011; moderate-to-severe airflow limitation, as indicated by post-bronchodilator FEV1 $\geq$ 30% and < 80% of the predicted normal and a post-bronchodilator FEV1/FVC ratio < 0.70 at run-in; current or ex-smokers, smoking history of at least 10 pack-years; symptomatic, as defined by a mMRC dyspnoea scale, Grade $\geq$ 2 **Exclusion criteria** History of asthma or concomitant pulmonary disease or with a significant disease other than COPD that could significantly confound the trial results or preclude trial completion (including cardiovascular, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities); COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalisation in the 6 weeks prior to visit 1

Interventions	1. Indacaterol/glycopyrrolate (27.5/15.6 μg twice daily); 1 capsule (between 0700-1100) and (between 1900-2300) 2. Indacaterol/glycopyrrolate (27.5/31.2 μg twice daily); 1 capsule (between 0700-1100) and (between 1900-2300) 3. Indacaterol (75 μg daily). **Inhaler device:** Neohaler **Allowed co-medications:** Each participant was provided with salbutamol/albuterol inhaler, which was permitted for use as rescue medication throughout study. Nebulised salbutamol/albuterol was not permitted. Participants had to use electronic diary to capture use of the rescue inhaler
Outcomes	AEs, bronchodilator effect on mean trough FEV1 pre-dose 15 min and 45 min at week 52 and on FEV1 and FVC at all post-baseline time points, vital signs, ECG, laboratory evaluations and time to first moderate or severe exacerbation, COPD symptoms reported and number of puffs/day of rescue medication during 52 week treatment
Notes	**Funding**: Novartis Pharmaceuticals Corp **Identifiers**: NCT01682863

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated to treatment group in a 1:1:1 ratio (with stratification for smoking status, ICS use, and severity of airflow limitation) using interactive response technology
Allocation concealment (selection bias)	Low risk	All eligible participants were randomised via interactive response technology (concealment assumed by automatisation)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind (participant, care provider, investigator, outcomes assessor)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind (participant, care provider, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was relatively high but even in the included arms, 13.2% in indacaterol/glycopyrrolate group and 11.6% in the indacaterol group. Efficacy was assessed in the full analysis set, which included all randomised participants who received at least one dose of the study drug; participants in

Ferguson 2016 (*Continued*)

		the full analysis set were analysed according to the treatment to which they were randomised
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the results summary on clinicaltrials.gov

Ferguson 2017

Methods	**Design:** phase 3B, 6-month, double-blind, double-dummy, randomised, parallel-group, multicentre exacerbation study **Duration:** 26 weeks **Location:** Argentina, Bulgaria, Chile, Czechia, Germany, Mexico, Poland, Puerto Rico, South Africa, Spain, USA
Participants	**Population** 1. Budesonide/formoterol 320/9 μg (606) 2. Formoterol 9 μg (613) **Baseline characteristics:** age 63.5 (SD 8.67) female:male 521:698 **Inclusion criteria** 1. Current clinical diagnosis of COPD with COPD symptoms for > 1 year, according to the GOLD criteria 2. Current or previous smoker with a smoking history equivalent to $\geq$ 10 pack-years (1 pack year = 20 cigarettes smoked per day for 1 year) 3. Post-bronchodilator FEV1/FVC < 0.7 (70%) and FEV1 $\leq$ 70% of predicted normal value 4. Documented use of a short-acting inhaled bronchodilator (β2-agonists or anticholinergics) as rescue medication within 6 months prior to study start 5. Score of $\geq$ 2 on the mMRC dyspnoea scale. 6. Documented history of $\geq$ 1 moderate or severe COPD exacerbation(s) that required treatment with systemic corticosteroids (a minimum 3-day course of an OCS treatment or single depot corticosteroid injection), or hospitalisation (defined as an inpatient stay or > 24-h stay in an observation area in the emergency department or other equivalent facility depending on the country and healthcare system) within 2-52 weeks before visit 1 (i.e. not within the 14 days prior to visit 1). A history of an exacerbation treated exclusively with antibiotics will not be considered adequate. **Exclusion criteria** 1. A history of asthma at or after 18 years of age. 2. Significant or unstable ischaemic heart disease, arrhythmia, cardiomyopathy, heart failure (including significant cor pulmonale), uncontrolled hypertension as defined by the investigator, or any other relevant cardiovascular disorder as judged by the investigator 3. Known homozygous alpha-1 antitrypsin deficiency 4. Any significant disease or disorder (e.g. gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, in the opinion of the investigator, may either put the participant at risk because of participation in the study, or influence the results of the study, or the participant's ability to participate in the study

	5. A history of malignancy (except basal cell carcinoma) within the past 5 years. 6. Active TB, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung disease, or other active pulmonary diseases. 7. Participants who have needed additions or alterations to their usual maintenance or change in formulation of rescue therapy for COPD due to worsening symptoms within the 14 days prior to visit 1 and up to Visit 3 8. A chest radiograph (frontal and lateral) with suspicion of pneumonia or other condition/abnormality that will require additional investigation/treatment, or put the participant at risk because of participation in the study 9. Risk factors for pneumonia: immune suppression (HIV, lupus) or other risk for pneumonia (e.g. neurological disorders affecting control of the upper airway, such as Parkinson's disease, and myasthenia gravis.) 10. Pneumonia not resolved within 14 days of visit 1 11. Moderate/severe COPD exacerbation that has not resolved within 14 days prior to visit 1 or a moderate/severe COPD exacerbation that occurs between visit 1 and Visit 2 12. LTOT or nocturnal oxygen therapy required for > 12 h/d 13. Participants who are currently in the intensive rehabilitation phase or scheduled to begin new participation (intensive rehabilitation phase) in a pulmonary rehabilitation programme during the study or have started a new pulmonary rehabilitation program within 60 days of visit 1. Participants in the maintenance phase of pulmonary rehabilitation programme are not excluded. 14. Treatment with oral, parenteral, or intra-articular corticosteroids within 4 weeks prior to visit 1 15. Omalizumab or any other monoclonal or polyclonal antibody therapy taken for any reason within 6 months prior to visit 1
Interventions	**Inhaler device:** 1. Budesonide/formoterol: pressurised MDI 2. Formoterol: Turbohaler **Allowed co-medications:** albuterol/salbutamol for as-needed rescue, ICS at a dose of $\leq$ 1000 μg·day
Outcomes	**Primary:** rate of moderate and severe COPD exacerbations defined as: worsening of $\geq$ 2 major symptoms or worsening of 1 major symptom together with $\geq$ 1 minor symptom for $\geq$ 2 consecutive days
Notes	**Funding:** AstraZeneca **Identifiers:** NCT02157935, D589UC00001

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system

Ferguson 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind (presumed participants and personnel/investigators)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout was relatively low but uneven between two groups (budesonide/formoterol 6.4%, formoterol 10.6%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Fukuchi 2013

Methods	**Design:** double-blind, parallel-group, active-controlled, phase 3 study **Duration:** 12 weeks **Location:** 163 centres in 9 countries (India, Japan, Korea, Philippines, Poland, Russia, Taiwan, Ukraine, Vietnam)
Participants	**Population:** 1293 randomised to 1. Budesonide/formoterol (636) 2. Formoterol (657) **Baseline characteristics** Age (mean): budesonide/formoterol (64.5), formoterol (65.6) Male (%): budesonide/formoterol (87.6), formoterol (90.3) FEV1 L (post bronchodilator): budesonide/formoterol (1.14), formoterol (1.11) Current smokers (%): budesonide/formoterol (33.8), formoterol (34.8) **Inclusion criteria** Male and female, aged ≥ 40 years with a diagnosis of moderate-severe COPD for at least 2 years (pre-bronchodilator FEV1 50% of predicted normal, post-bronchodilator FEV1/FVC < 70%), a current or previous smoking history of 10 pack-years, and having at least one COPD exacerbation in the 12 months prior to study entry were eligible to participate in the study **Exclusion criteria** History or current clinical diagnosis of asthma or atopic disease such as allergic rhinitis; significant or unstable ischaemic heart disease, arrhythmia, cardiomyopathy, heart failure, uncontrolled hypertension or any other relevant cardiovascular disorder; experiencing a COPD exacerbation during the run-in period or within 4 weeks prior to randomisation

	that required hospitalisation and/or a course of oral or parenteral steroids and requiring regular oxygen therapy were excluded
Interventions	1. Budesonide/formoterol 160/4.5 μg, 2 inhalations twice daily 2. Formoterol 4.5 μg, 2 inhalations twice daily **Inhaler device:** Turbuhaler **Allowed co-medications:** salbutamol 100 μg/actuation was available as reliever medication through the treatment period. In the case of a COPD exacerbation, participants were permitted any medication considered necessary for their patient's safety and well-being at the discretion of the investigator
Outcomes	Change in pre-dose FEV1 from baseline to the treatment period, 1 h post-dose, pre-dose and 1 h post-dose FVC, COPD symptoms (breathlessness, cough, night-time awakenings due to symptoms, time to first COPD exacerbation, number of COPD exacerbations (defined as a worsening in symptoms requiring treatment with a course of systemic steroid or hospitalisation), health-related QoL (SGRQ) and morning and evening PEF
Notes	**Funding:** AstraZeneca **Identifiers:** NCT01069289

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised 1:1 ratio to either treatment group. Sequence generation not described, but industry-funded so presumed electronic
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind (participant, care provider, investigator, outcomes assessor)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind (participant, care provider, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was low and relatively even in the included groups (8.5% in the formoterol group and 6.6% in the budesonide/formoterol group). The analysis set for efficacy was based on the full analysis set. Available data represent participants who had both baseline and on-treatment data, which is required to be included in the analysis

Selective reporting (reporting bias)	Low risk	Full results were available from the published report and on clinicaltrials.gov in accordance with the protocol

GLOW4 2012

Methods	**Design:** multicentre, randomised, open-label, parallel-group study **Duration:** 52 weeks **Location:** Japan
Participants	**Population** 1. Glycopyrrolate 50 μg (123) 2. Tiotropium 18 μg (40) **Baseline characteristics:** age 68.7 (SD 7.32), female:male 4:159 **Inclusion criteria** 1. Moderate-severe stable COPD (stage 2 or stage 3) according to the Gold 2008 criteria 2. Current or ex-smokers who have a smoking history of at least 10 pack-years 3. Post-bronchodilator FEV1 $\geq$ 30% and < 80% of the predicted normal, and postbronchodilator FEV1/FVC < 0.7 at Visit 2 (day -7) **Exclusion criteria** 1. Pregnant women or nursing mothers or women of child-bearing potential not using an acceptable method of contraception 2. LTOT 3. Lower respiratory tract infection within 6 weeks prior to visit 1 4. Concomitant pulmonary disease 5. History of asthma 6. Lung cancer or a history of lung cancer 7. History of certain cardiovascular comorbid conditions 8. Known history and diagnosis of alpha-1 antitrypsin deficiency 9. In active phase of a supervised pulmonary rehabilitation programme 10. Contraindicated for tiotropium or ipratropium treatment or who have shown an untoward reaction to inhaled anticholinergic agents 11. Other protocol-defined inclusion/exclusion criteria may apply
Interventions	**Inhaler device** 1. NVA237 (glycopyrronium): Breezhaler Powder for inhalation 2. Tiotropium: HandiHaler **Allowed co-medications:** as-needed albuterol
Outcomes	**Primary:** number of participants with AEs, SAEs or death
Notes	**Funding:** Novartis **Identifiers:** NCT01119937, CNVA237A1302

Risk of bias

Bias	Authors' judgement	Support for judgement

GLOW4 2012 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively low and even in both included groups (tiotropium 17.5%, glycopyrronium 15.4%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Hagedorn 2013

Methods	**Design:** randomised, open-label, parallel-group study **Duration:** 52 weeks **Location:** approximately 30 study centres in Germany
Participants	**Population** 1. Fluticasone propionate/salmeterol 500 μg/50 μg (108) 2. Fluticasone propionate 500 μg + salmeterol 50 μg (105) **Baseline characteristics:** age 64.9 (SD 8.6) female:male 62:180 **Inclusion criteria** 1. Diagnosis of COPD based on the ATS/ERS criteria 2. Male or female participants, aged $\geq$ 40 years. Women must be of non-child bearing potential 3. Have diagnosed COPD stage 3 or 4 according to GOLD criteria: a baseline post-bronchodilator FEV1 < 50% of predicted normal and a baseline post- bronchodilator FEV1/FVC ratio < 70% 4. Have experienced at least 2 moderate or severe COPD exacerbations leading to medical consultation (requiring OCS or increasing dosage of OCS and/or antibiotics or hospitalisation) within the 12 months preceding visit 1 5. Have stable COPD medication within 4 weeks prior to visit 1 (no new medication added and no dosage changes in medication) 6. Current or ex-smokers with a smoking history of at least 10 pack-years (number of pack-years = (number of cigarettes per day / 20) x number of years smoked, e.g. 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years) 7. Are currently managed at home (outpatients), are ambulatory and able to travel to the clinic. Participants can be treated with all relevant COPD medication. This includes vaccines, inhaled SABA as needed, short-acting or long-acting anticholinergics

	(tiotropium), systemic beta-2-agonists, theophylline, mucolytics, antioxidants, beta-1-agonists (for cardiovascular indication), non-invasive ventilation, LTOT and can have cor pulmonale. 8. A signed and dated written informed consent is obtained prior to participation. 9. Able to comply with the requirements of the protocol and be available for study visits over 52 weeks. **Exclusion criteria** 1. Known other respiratory disorders or signs for other respiratory disorders (e.g. asthma, lung cancer, sarcoidosis, TB, lung fibrosis, cystic fibrosis, bronchiectasis) 2. Known history of significant inflammatory disease, other than COPD (e.g. rheumatoid arthritis and systemic lupus erythematosus) 3. Known to be severely alpha-1-antitrypsin deficient (PI SZ or ZZ) 4. Having undergone lung surgery (e.g. lung resection including lung volume reduction surgery, lung transplant) or participants scheduled for surgery 5. Concurrent medication from visit 1 and for the duration of the study with any of the prohibited medications: monoamine oxidase inhibitors and tricyclic antidepressants, and ritonavir (a highly potent cytochrome P450 3A4 inhibitor) 6. Receiving chronic or prophylactic antibiotic therapy 7. Serious, uncontrolled disease (including serious psychological disorders) likely to interfere with the study or impact on participants' safety 8. Evidence of alcohol, drug or solvent abuse 9. History of depression 10. History or presence of clinically significant drug sensitivity or clinically significant allergic reaction to corticosteroids or salmeterol 11. Moderate or severe COPD exacerbation (requiring corticosteroids or increased dosage of corticosteroids and/or antibiotics or hospitalisation) within the 4 weeks prior to visit 1 12. Lower respiratory tract infection within the 4 weeks prior to visit 1 13. Pregnant or lactating female and female of childbearing potential 14. Participating investigator, subinvestigator, study co-ordinator, or other employee of a participating investigator, or is an immediate family member of the before mentioned; employee of GlaxoSmithKline (GSK) 15. Participated in an investigational drug study within 30 days prior to visit 1
Interventions	**Inhaler device** 1. Salmeterol/fluticasone (50 μg/500 µg) twice daily fixed combination 2. Salmeterol/fluticasone (50 μg/500 µg) twice daily separate inhalers comparator **Allowed co-medications:**
Outcomes	**Primary:** mean number of exacerbations per year: negative binomial model; mean number of exacerbations per year: Poisson model (baseline through week 52)
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT00527826, SCO107227

Risk of bias

Bias	Authors' judgement	Support for judgement

Hagedorn 2013 (*Continued)*

Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively high but even in both included groups (salmeterol/fluticasone propionate fixed 19.4% and 24.5% in salmeterol/fluticasone propionate free combo)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Hanania 2003

Methods	**Design**: double-blind, placebo-controlled, parallel-group, multicentre trial **Duration:** 24 weeks **Location:** 76 investigative sites in the USA
Participants	**Population:** 723 randomised to 1. fluticasone propionate 250 µg (183) - not included in this review. 2. salmeterol 50 µg (177) 3. fluticasone propionate + salmeterol in combination (178) 4. placebo (185) -not included in this review. **Baseline characteristics** Age (mean): placebo (65), salmeterol (64), fluticasone propionate (63), salmeterol/fluticasone (63) Male (%): placebo (68), salmeterol (58), fluticasone propionate (66), salmeterol/fluticasone (61) FEV1 L: placebo (1.289), salmeterol (1.245), fluticasone propionate (1.313), salmeterol/fluticasone (1.252) Current smokers (%): placebo (47), salmeterol (51), fluticasone propionate (48), salmeterol/fluticasone (43) **Inclusion criteria** Participants were $\geq$ 40 years of age, were current or former smokers with a $\geq$ 20 pack-year history, and had received a diagnosis of COPD, as defined by the ATS. Baseline FEV1/FVC ratio of $\leq$ 70% and a baseline FEV1 of < 65% of predicted normal, but > 0.70 L (or if $\leq$ 0.70 L, then > 40% of predicted normal); required to have symptoms of chronic bronchitis and moderate dyspnoea **Exclusion criteria**

	Current diagnosis of asthma; use of OCS within the past 6 weeks; abnormal clinically significant ECG; LTOT; moderate or severe exacerbation during the run-in period; and any significant medical disorder that would place the participant at risk, interfere with evaluations, or influence study participation
Interventions	**Inhaler device** 1. Fluticasone propionate 250 µg Flovent Diskus; GlaxoSmithKline, Inc) 2. Salmeterol 50 µg Serevent Diskus; GlaxoSmithKline, Inc 3. Salmeterol/Fluticasone 250 µg/50 µg Advair Diskus; GlaxoSmithKline, Inc) 4. Placebo Diskus (GlaxoSmithKline, Inc; Research Triangle Park, NC) **Allowed co-medications:** Ventolin inhalation aerosol or Ventolin nebules; GlaxoSmithKline, Inc)
Outcomes	Predose FEV1 and 2-h postdose FEV1; decreases in airway obstruction due to reduced inflammation measured by comparing changes in predose FEV1 between FSC and salmeterol; bronchodilation measured by changes in the 2-h postdose FEV1 between FSC and fluticasone propionate; morning PEF; dyspnoea (assessed by TDI); supplemental albuterol use; health status (assessed by the CRDQ) symptoms of chronic bronchitis (assessed by the CBSQ); exacerbations (defined by treatment, with moderate exacerbations requiring treatment with antibiotics and/or corticosteroids, and severe exacerbations requiring hospitalisation)
Notes	**Funding:** GlaxoSmithKline, Inc, **Identifiers:** SFCA3007

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by reversibility (defined as a 12% and 200 mL increase in FEV1 from baseline following the administration of 400 µg albuterol) and investigative site (sequence generation not described but study was industry-sponsored)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind (presumed participant and investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind (presumed participant and investigator). Reported outcomes not subject to detection bias (exacerbations, all-cause mortality, AEs and withdrawal)

Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 218 participants (placebo group, 32%; salmeterol group, 32%; fluticasone propionate group, 27%; and fluticasone propionate + salmeterol in combination group, 30%) were discontinued from the study. The breakdown of discontinuations were similar between fluticasone propionate + salmeterol in combination and salmeterol groups (GSK Clinical Study Report). In order to account for participant withdrawals, endpoint was used as the primary time point and was defined as the last on-treatment post baseline assessment excluding any data from the discontinuation visit
Selective reporting (reporting bias)	Low risk	All expected and stated outcomes were meticulously reported on the manufacturer's website as Clinical Study Report (https://www.gsk-clinicalstudyregister.com/files2/sfca3007-clinical-study-report-redact-v02.pdf)

Hanania 2017

Methods	**Design:** multicentre, randomised, double-blind, parallel-group, chronic-dosing, active-controlled, 28-week safety extension study **Duration:** 52 weeks total **Location:** Australia, New Zealand, USA
Participants	**Population** 1. Glycopyrronium/formoterol 14.4/9.6 μg (1036) 2. Glycopyrronium 14.4 μg (890) 3. Formoterol 9.6 μg (890) 4. Tiotropium 18 μg (451) **Baseline characteristics:** age 62.7 (SD 8.3) female:male 1439:1818 **Inclusion criteria** 1. Participant in/completion of previous 24-week PINNACLE phase 3 trial 2. Male or female participants at least 40 years of age and no older than 80 at visit 1 3. Participants with an established clinical history of COPD as defined by the ATS/ERS 4. Current or former smokers with a history of at least 10 pack-years of cigarette smoking 5. Participants with FEV1/FVC ratio of < 0.70 and FEV1 < 80% predicted normal and ≥ 750 mL if FEV1 < 30% of predicted normal value 6. Participants willing and, in the opinion of the investigator, able to adjust current COPD therapy as required by the protocol **Exclusion criteria**

	1. Significant diseases other than COPD, i.e. disease or condition which, in the opinion of the investigator, may put the participant at risk because of participation in the study or may influence either the results of the study or the participant's ability to participate in the study 2. Current diagnosis of asthma or alpha-1 antitrypsin deficiency 3. Other active pulmonary disease such as active TB, lung cancer, bronchiectasis, sarcoidosis, idiopathic interstitial pulmonary fibrosis, primary pulmonary hypertension, or uncontrolled sleep apnoea 4. Hospitalised due to poorly controlled COPD within 3 months prior to screening or during the screening period 5. Poorly controlled COPD, defined as acute worsening of COPD that requires treatment with OCS or antibiotics within 6 weeks prior to screening or during the screening period 6. Lower respiratory tract infections that required antibiotics within 6 weeks prior to screening or during the screening period 7. Unstable ischaemic heart disease, left ventricular failure, or documented MI within 12 months of enrolment 8. Recent history of acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass graft within the past 3 months 9. Congestive heart failure NYHA Class 3/4 10. Clinically significant abnormal 12-lead ECG 11. Abnormal liver function tests defined as ALT, AST, or total bilirubin $\geq$ 1.5 times ULN at visit 1 and on repeat testing 12. Cancer not in complete remission for at least 5 years 13. History of hypersensitivity to β2-agonists, glycopyrronium or other muscarinic anticholinergics, lactose/milk protein or any component of the MDI
Interventions	**Inhaler device** 1. Glycopyrronium/formoterol: MDI 2. Glycopyrronium: MDI 3. Fluticasone furorate: MDI 4. Open-label tiotropium: bromide inhalation powder 5. Placebo MDI **Allowed co-medications:** rescue albuterol, ICS, PDE4 inhibitor
Outcomes	**Primary:** CFB in morning-pre-dose trough FEV1 over 52 weeks
Notes	**Funding:** Pearl Therapeutics **Identifiers:** NCT01970878, PT003008-00

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details

Blinding of participants and personnel (performance bias) All outcomes	High risk	Tiotropium was open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Tiotropium was open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout relatively high but even among active comparators (glycopyrronium/formoterol 12.8%, glycopyrronium 12.4%, fluticasone furorate 12.2%, tiotropium 14.0%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Hoshino 2013

Methods	**Design:** A randomised, open-label, 4-way study **Duration:** 16 weeks **Location:** Shizuoka Japan
Participants	**Population** 1. Fluticasone propionate/salmeterol 250/50 µg (16) 2. Tiotropium 18 µg (15) 3. Salmeterol 50 µg (14) **Baseline characteristics:** age 71.2 female:male 8:52 **Inclusion criteria:** participants were patients > 40 years of age with a diagnosis of COPD, a cigarette smoking history > 10 pack-years, a postbronchodilator FEV 1 < 70% of the predicted value and ratio of FEV 1/FVC < 0.70 **Exclusion criteria**: a current diagnosis of asthma, a clinically significant medical disorder (other than COPD), supplemental use of oxygen for exertion or current use of some respiratory medications (including ICS, LABAs, tiotropium, theophylline or systemic corticosteroids)
Interventions	**Inhaler device** 1. Fluticasone propionate/salmeterol 250/50 μg twice daily 2. Tiotropium 18 μg once daily: HandiHaler 3. Salmeterol 50 μg twice daily **Allowed co-medications**: salbutamol was permitted when necessary to relieve symptoms. ICSs, theophylline and systemic corticosteroids were not allowed
Outcomes	Airway dimensions, as assessed by CT scans, the mean change in pulmonary function and SGRQ at 16 weeks
Notes	**Funding:** not described **Identifiers:** none provided

Hoshino 2013 *(Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Only airway dimensions were assessed in a blinded fashion
Incomplete outcome data (attrition bias) All outcomes	Low risk	68 participants were randomised and 60 of them completed the study (12% dropout rate)
Selective reporting (reporting bias)	Unclear risk	We could not locate a prospectively registered protocol to check all outcomes were reported

Hoshino 2014

Methods	**Design:** randomised, open-label, 3-way clinical trial **Duration:** 16 weeks **Location:** Shizuoka Japan
Participants	**Population:** 54 patients were randomised to 1. tiotropium 18 µg once daily (16) 2. indacaterol 150 µg once daily (20) 3. tiotropium + indacaterol once daily (18) **Baseline characteristics** Age (mean): tiotropium (73), indacaterol (69), tiotropium + indacaterol (71) Male (%): tiotropium (100), indacaterol (90), tiotropium + indacaterol (88) FEV1 L: tiotropium (1.48), indacaterol (1.63), tiotropium + indacaterol (1.46) Smoking (pack-years): tiotropium (63.4), indacaterol (62.8), tiotropium + indacaterol (57.8) **Inclusion criteria** The participants were all ex-smokers, > 40 years of age with a diagnosis of COPD, a cigarette smoking history of > 10 pack-years, a post-bronchodilator FEV1 < 70% of the predicted value, and an FEV1/FVC < 0.70 **Exclusion criteria:** current diagnosis of asthma, supplemental use of oxygen for exertion or current use of some respiratory medications

Interventions	1. Tiotropium 18 µg once daily 2. Indacaterol 150 µg once daily 3. Tiotropium 18 µg + indacaterol 150 µg once daily **Inhaler device** 1. Tiotropium: HandiHaler (Boehringer Ingelheim Pharma, Ingelheim, Germany) 2. Indacaterol: Breezhaler (Novartis, London, UK) **Allowed co-medications:** concurrent use of salbutamol was permitted when necessary to relieve symptoms
Outcomes	**Primary:** to evaluate the superiority of tiotropium + indacaterol treatment over tiotropium alone or indacaterol alone in its effect on airway dimensions **Secondary:** mean CFB in FEV1 and QoL to week 16. Pulmonary function, CT and assessment of QoL
Notes	**Funding:** unknown **Identifiers:** UMIN000006724

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Only CT interpretation was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rate was relatively low and even. 62 participants were randomised and 54 of them completed the study (13% dropout rate)
Selective reporting (reporting bias)	Low risk	Trial registration was located

Hoshino 2015

Methods	**Design:** randomised, open-label, parallel-group treatment study **Duration:** 16 weeks **Location:** Shizuoka Japan
Participants	**Population:** 46 patients were randomised to 1. tiotropium 18 μg once daily + indacaterol 150 μg once daily (24) 2. fluticasone propionate/salmeterol 250/50 μg twice daily (22) **Baseline characteristics** Age (mean): tiotropium + indacaterol (72), fluticasone propionate/salmeterol (69) Male (%): tiotropium + indacaterol (81), fluticasone propionate/salmeterol (86) FEV1 L: tiotropium + indacaterol (1.38), fluticasone propionate/salmeterol (1.36) Smoking (pack-years): tiotropium + indacaterol (56.2), fluticasone propionate/salmeterol (60.4) **Inclusion criteria** The participants were all ex-smokers > 40 years of age with a diagnosis of COPD; a cigarette smoking history > 10 pack-years; a post-bronchodilator FEV1 between 30%-80% of predicted value, and FEV1/FVC < 0.70 **Exclusion criteria:** current diagnosis of asthma; clinically significant medical disorder other than COPD; supplemental use of oxygen for exertion; or exacerbation needing treatment with antibiotics, systemic glucocorticosteroids
Interventions	1. Tiotropium (18 μg once daily) + indacaterol (150 μg once daily) 2. Fluticasone propionate/salmeterol (50/250 μg twice daily) **Inhaler device** 1. Tiotropium: HandiHaler (Boehringer Ingelheim Pharma, Ingelheim, Germany) 2. Indacaterol: Breezhaler (Novartis, London, UK) 3. Advair (Glaxo Smith Kline, London, UK) **Allowed co-medications:** rescue inhaler salbutamol 200 μg (Ventolin, Glaxo Smith Kline, London, UK) was permitted when necessary to relieve symptoms throughout study
Outcomes	**Primary:** to demonstrate superiority of tiotropium + indacaterol compared with Advair® for the effect on airway dimensions **Secondary:** to compare the effect of tiotropium + indacaterol versus Advair® on bronchodilator effect and health status during the treatment period. Pulmonary function, CT and assessment of QoL
Notes	**Funding:** not described. **Identifiers:** none provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Hoshino 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Only airway dimensions were assessed in a blinded fashion.
Incomplete outcome data (attrition bias) All outcomes	Low risk	54 participants were randomised and 46 of them completed the study (15% dropout rate)
Selective reporting (reporting bias)	High risk	We could not locate a prospectively registered protocol to check all outcomes were reported. SGRQ outcomes not described in detail

Jones 2011

Methods	**Design:** pooled data from three RCTs(Donohue 2010; Dahl 2010; Kornmann 2011) **Duration:** 6 months **Location:** 1. Donohue 2010: Argentina, Chile, Colombia, Czech Republic, Denmark, Ecuador, Egypt, Estonia, France, Germany, Hungary, Israel, Italy, Republic of Korea, Latvia, Lithuania, Netherlands, Peru, Romania, Russian Federation, Slovakia, Spain, Switzerland, Turkey, UK 2. Dahl 2010: Argentina, Canada, Germany, India, Italy, Republic of Korea, Puerto Rico, Spain, Sweden, Taiwan, Turkey, USA 3. Kornmann 2011: Belgium, New Zealand, USA
Participants	**Population** 1. Tiotropium 18 μg (345) 2. Formoterol 12 μg (385) 3. Salmeterol 50 μg (284) 4. Indacaterol 150 μg (620) 5. Indacaterol 300 μg (671) **Baseline characteristics:** age 64 (SD 9), female:male 31:69% **Inclusion/exclusion criteria:** See Donohue 2010; Dahl 2010; Kornmann 2011
Interventions	1. Tiotropium 18 μg once daily 2. Formoterol 12 μg twice daily 3. Salmeterol 50 μg twice daily 4. Indacaterol 150 μg once daily 5. Indacaterol 300 μg once daily **Inhaler device** 1. Dry powder Turbuhaler 2. Single-dose DPI (indacaterol) **Allowed co-medications:** as-needed albuterol, ICS

Outcomes	SGRQ responder at 6 months from 3 studies combined (Donohue 2010; Dahl 2010; Kornmann 2011)
Notes	**Funding:** Novartis **Identifiers:** NCT00393458 (Dahl 2010), NCT00463567 (Donohue 2010), and NCT00567996 (Kornmann 2011)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised to treatment (1:1:1:1) with stratification for smoking status (current/ex-smoker) using an automated interactive system
Allocation concealment (selection bias)	Low risk	Using an automated interactive system (concealment assumed by automatisation)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Protocol states double-blind for participant, caregiver, investigator and outcomes assessor http://www.clinicaltrials.gov/ct2/show/NCT00393458
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy results are presented for the modified ITT population including all randomised participants who received at least 1 dose of study drug. Withdrawal relatively high but reasons for dropout were similar across the active comparators
Selective reporting (reporting bias)	Low risk	All stated and expected outcomes reported in detail

Kalberg 2016

Methods	**Design:** multicentre, randomised, blinded, triple-dummy, parallel-group study **Duration:** 14 weeks **Location:** 86 centres across Argentina, Chile, Estonia, France, Germany, Hungary, Italy, Peru, Poland, Romania, the Russian Federation and Slovakia
Participants	**Population:** 961 patients were randomised 1. Umeclidinium/vilanterol (482) 2. Tiotropium + indacaterol (479)

Kalberg 2016 (*Continued)*

	Baseline characteristics Age (mean): umeclidinium/vilanterol (64), tiotropium + indacaterol (64) Male (%): umeclidinium/vilanterol (74), tiotropium + indacaterol (71) FEV1 L (pre bronchodilator): umeclidinium/vilanterol (1.369), tiotropium + indacaterol (1.357) Current smokers (%): umeclidinium/vilanterol (41), tiotropium + indacaterol (46) **Inclusion criteria** Participants were ≥ 40 years of age; had an established clinical history of COPD, were current or former cigarette smokers with a history of smoking of ≥ 10 pack-years; had pre- and post-bronchodilator FEV1 values of ≤ 70 % predicted; had pre- and postbronchodilator FEV1/FVC ratios of < 0.70; had a score of ≥ 2 on the mMRC l Dyspnea Scale; and had a QTc interval (corrected for the heart rate, according to Fridericia's formula) of < 450 or < 480 ms for participants with bundle branch block **Exclusion criteria** Participants were excluded from the study if they were of childbearing potential (unless they were practicing acceptable birth control methods); had a current diagnosis of asthma; had alpha-1 antitrypsin deficiency, an active lung infection (such as TB), lung cancer, or another clinically significant disease/abnormality; abnormal ECG; had a history of allergy or hypersensitivity to specific medications, had been hospitalised for COPD or pneumonia within 12 weeks prior to visit 1; had undergone lung volume reduction surgery within 12 months prior to visit 1; were receiving LTOT; or were enrolled actively in pulmonary rehab
Interventions	1. Umeclidinium/vilanterol 62.5/25 μg once daily + placebo (HandiHaler) + placebo (Breezehaler) 2. Tiotropioum 18 μg once daily via a HandiHaler + indacaterol 150 μg once daily via a Breezhaler + placebo (Ellipta inhaler) **Inhaler device** 1. Ellipta 2. HandiHaler 3. Breezhaler **Allowed co-medications:** all participants had albuterol provided for as-needed use
Outcomes	**Primary:** to determine whether the efficacy of umeclidinium/vilanterol was non-inferior to that of tiotropium + indacaterol as assessed by the trough FEV1 **Secondary:** weighted mean FEV1 over 0-6 h postdose at day 84, calculated from the predose FEV1 values (obtained 30 and 5 min before dosing) and the postdose FEV1 measurements at 1, 3, and 6 h
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT02257385; GSK116961

Risk of bias

Bias	Authors' judgement	Support for judgement

Kalberg 2016 (*Continued*)

Random sequence generation (selection bias)	Low risk	Participants were randomised in accordance with a centralised randomisation schedule, using a randomisation code generated by a validated computerised system (RandAll Version NG, GSK). Participants were randomised using an interactive voice-recognition system
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	All participants and investigators were blinded to the assigned treatment during the study. However, exact physical placebo matches for the tiotropium and indacaterol capsules and for the indacaterol blister packs were not available, although they were closely matched in colour
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Safeguards were in place to prevent the unblinding of study personnel, and study blinding co-ordinators independent of other clinical trial procedures were involved in the preparation and administration of treatment to participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	In total, 917 participants (95%) completed the study. The most common reason for study withdrawal was AEs, which accounted for a similar proportion of participants withdrawing from each treatment group
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

Kardos 2007

Methods	**Design:** randomised, double-blind, parallel-group study **Duration:** 44 weeks **Location:** 95 respiratory centres in Germany
Participants	**Population:** 994 participants were randomised to 1. salmeterol/fluticasone 50 μg/500 μg twice daily (507) 2. salmeterol 50 μg twice daily (487) **Baseline characteristics** Age (mean): salmeterol/fluticasone (63.8), salmeterol (64) Male (%): salmeterol/fluticasone (74), salmeterol (77.6) FEV1 L (pre bronchodilator): salmeterol/fluticasone (1.13), salmeterol (1.12)

	Current smokers (%): salmeterol/fluticasone (40.6), salmeterol (44.4) **Inclusion criteria:** outpatients with severe COPD, defined according to GOLD stages 3 and 4, FEV1/FVC of ≤ 70%, age of ≥ 40 years, smoking history of ≥ 10 pack-years, history ≥ 2 exacerbations in the last year before the study **Exclusion criteria:** COPD exacerbations, hospital admissions, or change in COPD therapy during the 4 weeks before visit 1 or run-in period. Asthma, need for LTOT or chronic systemic steroid
Interventions	**Inhaler device** 1. Diskus (GlaxoWellcome GmbH&Co, Bad Oldesloe, Germany) **Allowed co-medications:** inhaled salbutamol was used as reliever medication, and regular treatment with short-acting bronchodilators, antioxidants/mucolytics, oral SABAs, and theophylline
Outcomes	**Primary:** number of moderate and severe exacerbations in each treatment group **Secondary:** time to first exacerbation, prebronchodilator PEF, post-bronchodilator FEV1, and disease-specific QoL as evaluated by the SGRQ, which investigated 3 different domains consisting of activity, symptom, and impact scores
Notes	**Funding:** GlaxoSmithKline **Identifiers:** SCO30006

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Consecutive numbers were assigned to participants that determined the blinded treatment based on a centrally generated list with blocks of 6. Industry-funded
Allocation concealment (selection bias)	Low risk	Consecutive numbers were assigned to participants that determined the blinded treatment based on a centrally generated list with blocks of 6
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind (presumed participant and investigator)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the study population, there were 99 withdrawals (19.5%) in the salmeterol/fluticasone group and 103 (21.1%) in the salmeterol group, both mainly due to AEs that were primarily linked to COPD deteriora-

Kardos 2007 (*Continued)*

		tion
Selective reporting (reporting bias)	Unclear risk	Unable to locate protocol to check outcome reporting

Kerwin 2012a

Methods	**Design:** randomised, double-blind, placebo-controlled, parallel-group study, with open-label tiotropium **Duration:** 52 weeks **Location:** 170 centres in 18 countries: Argentina, Canada, Chile, France, Germany, Hungary, Israel, Italy, Korea, Mexico, Netherlands, New Zealand, Peru, Poland, Russia, South Africa,Thailand, USA
Participants	**Population:** 1066 patients were randomised to 1 of 3 study groups: 1. glycopyrronium bromide (NVA237) 50 μg daily (529) 2. tiotropium 18 μg daily (268) 3. placebo (269) **Baseline characteristics** Age (mean): glycopyrronium bromide 63.5 (SD 9.1), placebo 63.6 SD 9.1), tiotropium 63.9 (SD 8.2) Male (%): glycopyrronium bromide (64.6), placebo (64.6), tiotropium (62.9) FEV1 L (pre bronchodilator): glycopyrronium bromide 1.3 (SD 0.5), placebo (1.4 SD 0.5), tiotropium 1.3 (SD 0.5) Current smokers (%): glycopyrronium bromide (45.3), placebo (46.3), tiotropium (44.2) **Inclusion criteria** $\geq$ 40 years of age, with a smoking history of $\geq$ 10 pack-years, a diagnosis of moderate-severe stable COPD, post-bronchodilator FEV1 $\geq$ 30% and < 80% of the predicted normal, and postbronchodilator FEV1/FVC < 0.70 were enrolled **Exclusion criteria:** lower respiratory tract infection in the 6 weeks prior to screening; concomitant pulmonary disease, history of asthma, malignancy of any organ system, long QT syndrome at screening, symptomatic prostatic hyperplasia, bladder-neck obstruction, moderate/severe renal impairment, urinary retention, narrow-angle glaucoma, a known history of α1-antitrypsin deficiency; participation in the active phase of a supervised pulmonary rehabilitation programme; and contraindications for tiotropium or ipratropium or history of adverse reactions to inhaled anticholinergics
Interventions	**Inhaler device:** 1. Glycopyrronium bromide (NVA237) via Breezhaler® device 2. Placebo via Breezhaler® device 3. Tiotropium via HandiHaler® device **Allowed co-medications:** inhaled or intranasal corticosteroids and H1 antagonists were permitted in participants who had been stabilised on a recommended and constant dose prior to study entry. Participants were provided with a salbutamol/albuterol inhaler to be used as rescue medication during the study
Outcomes	Trough FEV1 at week 12, dyspnoea, QoL, exacerbations

Kerwin 2012a (*Continued*)

Notes	**Funding:** Novartis **Identifiers:** NCT00929110

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised 2:1:1 ratio (sequence generation not described, but industry-funded so presumed electronic)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was relatively high but even between included groups (22.3% in glycopyrronium and 23.1% in tiotropium group) . Efficacy was assessed in the FAS, which included all randomised participants who received at least one dose of the study drug; participants in the FAS were analysed according to the treatment to which they were randomised
Selective reporting (reporting bias)	Low risk	Full results in the published report and on clinicaltrials.gov in accordance with the protocol

Kerwin 2017

Methods	**Design:** randomized, double-dummy, parallel group, multicenter trial **Duration:** 12 weeks **Location:** Argentina, Estonia, Germany, Korea, Republic of, Norway, Russian Federation, South Africa, Sweden, Ukraine, United States
Participants	**Population** 1. Umeclidinium/Vilanterol 62.5/25 μg (247) 2. Tiotropium 18 μg) (247) **Baseline characteristics:** age 64.4 (SD 8.71), female:male 171:323 **Inclusion criteria** 40 years of age with a diagnosis of COPD according to the American Thoracic Society/

	European Respiratory Society definition, a post-salbutamol FEV1 of < 70% and >50% of normal predicted values, a mMRC Dyspnea Scale score of >1 at screening, and tiotropium was prescribed for at least 3 months prior to screening **Exclusion criteria** use of ICS or maintenance COPD medications other than tiotropium in the 3 months prior to screening (including other LAMAs, LABAs, LAMA/LABA combinations, ICS/LABA combinations, phosphodiesterase-4 inhibitors, theophyllines, and oral β2-agonists), a current diagnosis of asthma, respiratory diseases other than COPD considered clinically significant by the study investigator, and more than one moderate-to-severe COPD exacerbation in the past 12 months
Interventions	**Inhaler device** 1. Umeclidinium/Vilanterol Inhalation Powder 2. Tiotropium Inhalation Powder **Allowed co-medications:** as-needed albuterol
Outcomes	**Primary:** Change from baseline in trough FEV1 on Day 85
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01899742, DB2116960

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized in a 1:1 ratio using a random code generator and assigned to treatment group via an interactive voice/web recognition system
Allocation concealment (selection bias)	Low risk	Patients were randomized in a 1:1 ratio using a random code generator and assigned to treatment group via an interactive voice/web recognition system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	blinded, double-dummy study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Staff involved with safety and efficacy assessments were not present during dosing in the clinic to maintain blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates were low and even in both included groups (6.9 % in umeclidinium/vilanterol group and 6.5% in tiotropium group)

Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Koch 2014

Methods	**Design:** phase 3, multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group studies **Duration:** 48 weeks **Location:** Argentina, Brazil, Canada, Croatia, Czech Republic, Denmark, Finland, Germany, Hong Kong, India, Italy, Korea, Republic of, Malaysia, Norway, Philippines, South Africa, Spain, Sweden, Thailand, Ukraine
Participants	**Population** 1. Study 1222.13: olodaterol (5 μg) 227, formoterol (12 μg) 227 2. Study 1222.14: olodaterol (5 μg) 232, formoterol (12 μg) 233 **Baseline characteristics** 1. Study 1222.13 age 63.8 (8.7) female:male 198:706. 2. Study 1222.14 age 64.2 (SD 8.7) female:male 176:758 **Inclusion criteria** 1. Diagnosis of COPD with post-bronchodilator FEV1 < 80% of predicted normal and a post-bronchodilator FEV1/FVC < 70% at visit 1 2. Male or female, ≥ 40 years of age 3. Current or ex-smokers with a smoking history of > 10 pack-years **Exclusion criteria** 1. Clinically relevant abnormal baseline haematology, blood chemistry, or urinalysis; all participants with an SGOT > x2 ULN, SGPT > x2 ULN, bilirubin > x2 ULN or creatinine > x2 ULN 2. History of asthma and/or total blood eosinophil count > 600/mm^3 3. Thyrotoxicosis, paroxysmal tachycardia (> 100 BPM) 4. History of MI within 1 year of screening visit, unstable or life-threatening cardiac arrhythmia, hospitalisation for heart failure within the past year, known active TB, a malignancy for which patient has undergone resection, radiation therapy or chemotherapy within last 5 years, life-threatening pulmonary obstruction, cystic fibrosis, clinically evident bronchiectasis, significant alcohol or drug abuse 5. Previous thoracotomy with pulmonary resection 6. Currently being treated with oral beta-adrenergics or OCS medication at unstable doses (i.e. < 6 weeks on a stable dose), or at doses > the equivalent of 10 mg of prednisone/d or 20 mg every other day. 7. Regular use of daytime oxygen therapy for > 1 h/d 8. Completed a pulmonary rehabilitation programme in the 6 weeks prior to the screening visit (visit 1) or currently in a pulmonary rehabilitation programme 9. Pregnant or nursing women 10. Women of childbearing potential not using two effective methods of birth control (one barrier and one non-barrier)
Interventions	**Inhaler device:** 1. Olodaterol via Respimat 2. Formoterol Aerolizer inhaler

	Allowed co-medications: albuterol as needed, short-acting antimuscarinic agents, LAMAs, ICS, and xanthines
Outcomes	FEV1, TDI, SGRQ
Notes	**Funding:** Merck **Identifiers:** NCT00793624, NCT00796653, 1222.13, 1222.14

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively low in both included groups (olodaterol16%, formoterol 12%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Kornmann 2011

Methods	**Design:** randomised, double-blind, placebo-controlled, parallel-group study **Duration:** 26 weeks **Location:** 142 centres in 15 countries (Canada, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Iceland, India, Italy, Peru, Russian Federation, Slovakia, Taiwan)
Participants	**Population:** 998 patients were randomised to 1. indacaterol 150 μg daily (333) 2. salmeterol 50 μg twice daily (334) 3. placebo (335) - not included in this review. **Baseline characteristics** Age (mean): indacaterol 63 (SD 8.7), salmeterol 63 (SD 9.2), placebo 64 (SD 8.6) Male (%): indacaterol (72), salmeterol (75), placebo (77) FEV1 L (pre BD): indacaterol 1.5 (SD 0.49), salmeterol 1.5 (SD 0.49), placebo 1.5 (SD 0.47)

Kornmann 2011 (*Continued)*

	Current smokers (%): indacaterol (46), salmeterol (46), placebo (45) **Inclusion criteria:** ≥ 40 years with clinical diagnosis of moderate-severe COPD and smoking history of ≥ 20 pack-years **Exclusion criteria:** asthma
Interventions	**Inhaler device:** DPI **Allowed co-medications:** participants were permitted concomitant medication with ICS, if dose and regimen were stable for 1 month prior to screening. Salbutamol was provided for use as needed (but not < 6 h before study assessments)
Outcomes	Trough FEV1 after 12 weeks, efficacy outcomes, safety and tolerability
Notes	**Funding:** Novartis **Identifiers:** NCT00567996

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1:1:1 ratio (with stratification for smoking status) using an automated system
Allocation concealment (selection bias)	Low risk	Automated system used for randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple (participant, investigator, outcomes assessor)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Triple (participant, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was relatively low and even between active comparators (13.2% in indacaterol and 15.0% in salmeterol group)
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the results summary on clinicaltrials.gov

Koser 2010

Methods	**Design:** randomised, double-blind, parallel-group study **Duration:** 12 weeks **Location:** 16 research sites in the USA
Participants	**Population:** 247 patients were randomised to 1. Fluticasone propionate/salmeterol 250/50 μg twice-daily (126) 2. Fluticasone propionate/salmeterol hydrofluoroalkane 230/42 μg (121) **Baseline characteristics**

	Age (mean): fluticasone propionate/salmeterol Diskus (63.4), fluticasone propionate/salmeterol MDI (61.6) Male (%): fluticasone propionate/salmeterol Diskus (52), fluticasone propionate/salmeterol MDI (55) FEV1 L (pre bronchodilator): fluticasone propionate/salmeterol Diskus (1.39), fluticasone propionate/salmeterol MDI (1.47) Current smokers (%): fluticasone propionate/salmeterol Diskus (62), fluticasone propionate/salmeterol MDI (61) **Inclusion criteria** 1. Diagnosis of COPD 2. Current or former smokers with at least a 10 pack-year history 3. Aged > 40 years 4. Post-bronchodilator FEV1 of > 0.70 L and < 70% predicted normal (or if FEV1 < 0.70 L, then > 40% of predicted normal value), and a post-albuterol FEV1/FVC ratio of < 0.70 **Exclusion criteria** 1. Asthma 2. Clinically significant and uncontrolled medical disorder 3. COPD exacerbation/infection that required corticosteroids and/or antibiotics that did not resolve within 30 days of visit 1 4. Abnormal ECG at screening 5. BMI > 40kg/m^2 6. Use of nocturnal positive pressure such as CPAP or BiPAP
Interventions	**Inhaler device:** 1. Fluticasone propionate/salmeterol: Diskus 2. Fluticasone propionate/salmeterol hydrofluoroalkane: MDI **Allowed co-medications:** none
Outcomes	Mean CFB in FEV1 2 h post-dose, mean CFB in morning pre-dose FEV1 and PEF
Notes	**Funding:** GlaxoSmithKline **Identifiers:**NCT00633217, ADC111117

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised treatment assignment was provided to the investigative site by means of an interactive voice-response system at the time participants were randomised
Allocation concealment (selection bias)	Low risk	Randomised treatment assignment was provided to the investigative site by means of an interactive voice-response system at the time participants were randomised

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (participant and investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind (participant and investigator)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rates 12.4% in the fluticasone propionate/salmeterol hydrofluoroalkane and 18.3 % in the Diskus group. Reasons for dropout were similar between 2 groups The primary analysis population was the ITT population
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

Mahler 2002

Methods	**Design:** randomised, double-blind, placebo-controlled, parallel-group study **Duration:** 24 weeks **Location:** 64 centres in the USA
Participants	**Population:** 674 patients were randomised to 4 arms 1. fluticasone 500 μg (168) - not included in this review. 2. salmeterol 50 μg (160) 3. fluticasone/salmeterol 500/50 μg (165) 4. placebo (181) - not included in this review. **Baseline characteristics** Age (mean): placebo (64), salmeterol (63.5), fluticasone (64.4), fluticasone/salmeterol (61.9) Male (%): placebo (75), salmeterol (64), fluticasone (61), fluticasone/salmeterol (62) FEV1 L (pre BD): placebo (1.317), salmeterol (1.237), fluticasone (1.233), fluticasone/salmeterol (1.268) Current smokers (%): placebo (54), salmeterol (46), fluticasone (46), fluticasone/salmeterol (46) **Inclusion criteria:** $\geq$ 40 years of age, were current or former smokers with $\geq$ 20 pack-year history, and COPD. Baseline FEV1/FVC of < 70% and a baseline FEV1 < 65% of predicted but > 0.70 L. Participants were required to have daily cough productive of sputum for 3 months of the year for 2 consecutive years and dyspnoea **Exclusion criteria:** asthma, OCS use within the past 6 weeks, abnormal clinically significant ECG, LTOT, moderate or severe exacerbation during the run-in period
Interventions	**Inhaler device:** 1. Fluticasone propionate (Flovent Diskus GlaxoSmith-Kline) 2. Salmeterol (Serevent Diskus; Glaxo-SmithKline, Research Triangle Park,NC)

	3. Fluticasone/salmeterol (Advair Diskus; Glaxo-SmithKline) **Allowed co-medications:** albuterol as needed
Outcomes	Change in predose FEV1 values, change in 2-h postdose FEV1 values, morning PEF, supplemental albuterol use, dyspnoea, and exacerbations
Notes	**Funding:** GlaxoSmithKline **Identifiers:** SFCA3006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised treatment assignment was provided to the investigative site by means of an interactive voice-response system at the time participants were randomised
Allocation concealment (selection bias)	Low risk	Randomised treatment assignment was provided to the investigative site by means of an interactive voice-response system at the time participants were randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No details provided but outcomes not subject to detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 234 participants (38%, 28%, 40%, and 32% for placebo, salmeterol, fluticasone, and fluticasone/salmeterol groups, respectively). Reasons for withdrawal were similar across the groups. Dropouts addressed with various methods including multiple imputation, analysis of only completers, and recursive regression imputation
Selective reporting (reporting bias)	Low risk	Protocol was located. Outcomes were well reported

Mahler 2012a

Methods	**Design**: randomised, double-blind, controlled, parallel-group **Duration**: 12 weeks **Location**: 186 centres in 14 countries; Argentina (10), Australia (6), Colombia (5), Denmark (5), Germany (25), Greece (4), Guatemala (5), Mexico (5), Peru (6), Philippines (2), South Africa (6), Spain (13), Turkey (13) and USA (81)
Participants	**Population:** 1131 patients were randomised to 1. Tiotropium 18 μg + indacaterol 150 μg daily (570) 2. Tiotropium 18 μg + placebo daily (561) **Baseline characteristics:** age (mean): tiotropium + indacaterol (64), tiotropium + placebo (63.4) Male (%): tiotropium + indacaterol (70), tiotropium + placebo (67) FEV1 L (pre BD): tiotropium + indacaterol (1.15), tiotropium + placebo (1.15) Current smokers (%): tiotropium + indacaterol (40), tiotropium + placebo (36) **Inclusion criteria:** aged $\geq$ 40 years with moderate-severe COPD with a smoking history $\geq$10 pack-years and postbronchodilator FEV1 $\leq$ 65% and $\geq$ 30% of predicted normal, and post-bronchodilator FEV1/FVC < 70% at screening **Exclusion criteria:** history of asthma or had experienced a respiratory tract infection or COPD exacerbation within the previous 6 weeks
Interventions	**Inhaler device:** 1. Indacaterol/placebo via a single-dose DPI device 2. Tiotropium via HandiHaler® **Allowed co-medications:** salbutamol (albuterol in the USA) was available for as-needed use. Participants receiving ICS at baseline continued treatment (or were switched to ICS monotherapy if taken as a fixed combination with a bronchodilator) at equivalent dose and regimen during the study
Outcomes	FEV1 standardised (with respect to length of time) AUC from 5 min to 8 h post-dose at the end of treatment Trough FEV1 24 h post-dose at the end of treatment
Notes	**Funding:** Novartis Pharmaceuticals **Identifiers:** NCT00846586

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation (1:1) was performed using an automated interactive voice-response system and was stratified by COPD severity (moderate or severe), with balance maintained at country level
Allocation concealment (selection bias)	Low risk	Balance maintained at country level. Automated randomisation

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and staff at participating centres were unaware of treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, those performing the assessments and data analysts were blinded unless an emergency arose
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completion rates were similar (93%-94%) between treatment groups and studies
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

Mahler 2012b

Methods	**Design:** randomised, double-blind, controlled, parallel-group **Duration:** 12 weeks **Location:** 182 centres in 11 countries; Argentina (9), Canada (16), Colombia (3), Czech Republic (9), Hungary (4), India (9), Netherlands (6), Philippines (3), Slovakia (10), Spain (11), USA (102)
Participants	**Population:** 1142 patients were randomised to 1. tiotropium 18 μg + indacaterol 150 μg daily (572) 2. tiotropium 18 μg + placebo daily (570) **Baseline characteristics** Age (mean): tiotropium + indacaterol (63.1), tiotropium + placebo (62.8) Male (%): tiotropium + indacaterol (63), tiotropium + placebo (68) FEV1 L (pre BD): tiotropium + indacaterol (1.14), tiotropium + placebo (1.15) Current smokers (%): tiotropium + indacaterol (38), tiotropium + placebo (43) **Inclusion criteria:** aged $\geq$ 40 years with moderate-severe COPD with a smoking history $\geq$ 10 pack-years and postbronchodilator FEV1 $\leq$ 65% and $\geq$ 30% of predicted normal, and post-bronchodilator FEV1/forced vital capacity < 70% at screening **Exclusion criteria:** history of asthma or had experienced a respiratory tract infection or COPD exacerbation within the previous 6 weeks
Interventions	**Inhaler device:** 1. Indacaterol/placebo via a single-dose DPI device 2. Tiotropium via HandiHaler® **Allowed co-medications:** salbutamol (albuterol in the USA) was available for as-needed use. Participants receiving ICS at baseline continued treatment (or were switched to ICS monotherapy if taken as a fixed combination with a bronchodilator) at equivalent dose and regimen during the study
Outcomes	FEV1 standardised (with respect to length of time) AUC from 5 min to 8 h post-dose at the end of treatment

Notes	**Funding:** Novartis **Identifiers:** NCT00877383

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation (1:1) was performed using an automated interactive voice-response system and was stratified by COPD severity (moderate or severe), with balance maintained at country level
Allocation concealment (selection bias)	Low risk	Balance maintained at country level. Automated randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and staff at participating centres were unaware of treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, those performing the assessments and data analysts were blinded unless an emergency arose
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completion rates were high and similar (94%-95%) between treatment groups
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

Mahler 2015a

Methods	**Design:** randomised, double-blind, parallel-group, placebo and active-controlled studies **Duration:** 12 weeks **Location:** USA, Canada, Philippines, Poland, Romania, Spain, Ukraine and Vietnam
Participants	**Population:** patients were randomised into 1 of 4 arms (combined population from Mahler 2015a and Mahler 2015b) 1. Indacaterol/glycopyrrolate (indacaterol 27.5/15.6 μg twice daily) (508), 2. Indacaterol (indacaterol 27.5 μg twice daily) (511), 3. Glycopyrrolate (15.6 μg twice daily) (511) 4. Placebo (508) **Baseline characteristics (pooled analysis of Mahler 2015aand Mahler 2015b)** Age (mean): indacaterol/glycopyrronium (63.4), indacaterol (63.7), glycopyrronium (63.4), placebo (63.2) Male (%): indacaterol/glycopyrronium (63.4), indacaterol (65.8), glycopyrronium (63.8), placebo (60.2) FEV1 L (pre bronchodilator): indacaterol/glycopyrronium (1.264), indacaterol (1.280)

	, glycopyrronium (1.258), placebo (1.250) Current smokers (%): indacaterol/glycopyrronium (50.4), indacaterol (52.1), glycopyrronium (52.3), placebo (51.6) **Inclusion criteria:** $\geq$ 40 years of age; stable but symptomatic moderate-severe COPD according to the GOLD 2011 criteria; smoking history of at least 10 years **Exclusion criteria:** COPD exacerbation requiring antibiotics and/or systemic steroids in last 6 weeks prior to visit 1, long QT syndrome, respiratory tract infection within 4 weeks of screening, history of asthma
Interventions	**Inhaler device:** all treatments were delivered via the Neohaler device (Novartis Pharma AG, Basel, Switzerland) **Allowed co-medications:** participants continued to use fixed doses of ICSs if they had been previously prescribed. Albuterol MDI was allowed as rescue medication throughout the treatment period
Outcomes	Standardised AUC for FEV1 between 0-12 h at end of treatment period, also change in SGRQ total score from baseline and in the percentage of responders
Notes	**Funding:** Novartis **Identifiers:** NCT 01727141

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	All eligible participants were randomised via interactive response technology in 1:1: 1:1 ratio
Allocation concealment (selection bias)	Low risk	All eligible participants were randomised via interactive response technology in 1:1: 1:1 ratio
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, scheduling of administration, appearance, taste and odour
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completion rates were high and similar (97%-99%) among active comparators
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

Mahler 2015b

Methods	**Design:** randomised, double-blind, parallel-group, placebo and active-controlled studies **Duration:** 12 weeks **Location:** USA, Colombia, Egypt, France, Guatemala, Hungary, Panama, Slovakia and Slovenia
Participants	**Population:** patients were randomised into 1 of 4 arms (combined population from Mahler 2015a and Mahler 2015b) 1. Indacaterol/glycopyrrolate (indacaterol 27.5/15.6 μg twice daily) (508), 2. Indacaterol (indacaterol 27.5 μg twice daily) (511), 3. Glycopyrrolate (15.6 μg twice daily) (511) 4. Placebo (508) **Baseline characteristics (pooled analysis of Mahler 2015aand Mahler 2015b)** Age (mean): indacaterol/glycopyrronium (63.4), indacaterol (63.7), glycopyrronium (63.4), placebo (63.2) Male (%): indacaterol/glycopyrronium (63.4), indacaterol (65.8), glycopyrronium (63.8), placebo (60.2) FEV1 L (pre BD): indacaterol/glycopyrronium (1.264), indacaterol (1.280), glycopyrronium (1.258), placebo (1.250) Current smokers (%): indacaterol/glycopyrronium (50.4), indacaterol (52.1), glycopyrronium (52.3), placebo (51.6) **Inclusion criteria:** $\geq$ 40 years of age; stable but symptomatic moderate-severe COPD according to the GOLD 2011 criteria **Exclusion criteria:** COPD exacerbation requiring antibiotics and/or systemic steroids in last 6 weeks prior to visit 1, long QT syndrome, respiratory tract infection within 4 weeks of screening, history of asthma
Interventions	**Inhaler device:** all treatments were delivered via the Neohaler device (Novartis Pharma AG, Basel, Switzerland) **Allowed co-medications:** participants continued to use fixed doses of ICS if they had been previously prescribed. Albuterol MDI was allowed as rescue medication throughout the treatment period
Outcomes	Standardised AUC for FEV1 between 0-12 h at end of treatment period, also change in SGRQ total score from baseline and in the percentage of responders
Notes	**Funding:** Novartis **Identifiers:** NCT01712516

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All eligible participants were randomised via interactive response technology in 1:1:1:1 ratio
Allocation concealment (selection bias)	Low risk	All eligible participants were randomised via interactive response technology in 1:1:1:1 ratio

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, scheduling of administration, appearance, taste and odour
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completion rates were high and similar (96%-98%) among active comparators
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

Mahler 2016

Methods	**Design:** randomised, multicentre, double-blind, parallel-group study **Duration:** 52 weeks **Location:** 65 centres in the USA
Participants	**Population:** 507 patients were randomised to 1. Glycopyrronium 15.6 μg twice daily (251) 2. Indacaterol 75 μg daily (256) **Baseline characteristics:** Age (mean): glycopyrronium (63.3), indacaterol (63.2) Male (%): glycopyrronium (56.2), indacaterol (58.2) FEV1 L (pre BD): glycopyrronium (1.24), indacaterol (1.25) Current smokers (%): glycopyrronium (54.2), indacaterol (55.5) **Inclusion criteria:** aged $\geq$ 40 years with stable COPD (GOLD 2011 levels 2 and 3), who were current or ex-smokers with a smoking history of at least 10 pack-years, who presented with post-bronchodilator FEV1 $\geq$ 30% and < 80% of the predicted normal, and a post-bronchodilator FEV1/FVC < 0.70, and with a mMRC Dyspnea Scale grade of at least 2 **Exclusion criteria:** history of long QT syndrome, clinically significant ECG abnormality, clinically significant CVD, renal abnormalities, history of asthma, and COPD exacerbations that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalisation within the 6 weeks before the screening or during the screening and run-in periods
Interventions	**Inhaler device:** both treatment arms used low-resistance, single-dose, DPI (Neohaler™ device) **Allowed co-medications:** stable background treatment with ICS was permitted to be continued throughout the study. During the study, participants were provided with albuterol as a rescue medication

Outcomes	Safety and tolerability in terms of AE reporting rates. Time to first moderate or severe COPD exacerbations. Pre-dose trough FEV1 at week 52. FEV1 and FVC measurements at all post-baseline time points, and rescue medication use over 52 weeks of treatment period
Notes	**Funding:** Novartis **Identifiers:** NCT01697696

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A patient randomisation list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomisation numbers. A separate medication list was produced by Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to study drug packs containing each of the study drugs
Allocation concealment (selection bias)	Low risk	A patient randomisation list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomisation numbers. A separate medication list was produced by Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to study drug packs containing each of the study drugs
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quadruple masking (participant, care provider, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	Low risk	18% of participants discontinued the study before the end of treatment period, discontinuation rates and reasons were similar between both groups

Mahler 2016 (*Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

Maleki-Yazdi 2014

Methods	**Design:** multicentre, randomised, double-dummy, parallel-group study **Duration:** 24 weeks **Location:** 71 centres in 8 countries (Bulgaria, Canada, Germany, Hungary, Romania, Russia, Spain, and USA)
Participants	**Population:** 905 patients were randomised to 1. umeclidinium bromide + vilanterol 62.5/25 μg once-daily (454) 2. tiotropium 18 μg daily (451) **Baseline characteristics** Age (mean): umeclidinium/vilanterol (61.9), tiotropium (62.7) Male (%): umeclidinium/vilanterol (68), tiotropium (67) FEV1 L (post BD): umeclidinium/vilanterol (1.41), tiotropium (1.41) Current smokers (%): umeclidinium/vilanterol (59), tiotropium (54) **Inclusion criteria:** aged $\geq$ 40 years with moderate-very severe COPD and an established clinical history of COPD as defined by ATS/ERS guidelines **Exclusion criteria:** hospitalised for COPD or pneumonia within 12 weeks prior to visit 1
Interventions	**Inhaler device** 1. Umeclidinium/vilanterol via DPI, ELLIPTA DPI; 2. Tiotropium via Handi-Haler **Allowed co-medications:** use of albuterol/salbutamol provided by GlaxoSmithKline via MDI as relief medication was permitted, but was withheld for $\leq$ 4 h prior to spirometry testing. ICS at a consistent dose of up to 1000 μg/day of fluticasone propionate or equivalent were permitted and recorded
Outcomes	Trough FEV1 at day 169, weighted mean FEV1 over 0-6 h post-dose at day 168
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01777334, ZEP117115

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation code was generated using a GlaxoSmithKline validated computerised system, RandAll
Allocation concealment (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an au-

Maleki-Yazdi 2014 *(Continued)*

		tomated, interactive telephone-based system and the link to the randomisation schedule was kept confidential from all staff
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy design was used for retaining the blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator and treating physician were blinded till an emergency arose
Incomplete outcome data (attrition bias) All outcomes	Low risk	Most participants completed the study (88%, umeclidinium/vilanterol group; 86%, tiotropium group). Reasons for dropout were similar between 2 groups
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

Martinez 2017a

Methods	**Design:** randomised, double-blind, chronic-dosing, placebo-controlled, parallel-group, multicentre study **Duration:** 24 weeks **Location:** Australia, New Zealand, USA
Participants	**Population** 1. Glycopyrronium/formoterol 14.4/9.6 μg (526) 2. Glycopyrronium 14.4 μg (451) 3. Formoterol 9.6 μg (452) 4. Tiotropium (18 μg) (451) **Baseline characteristics:** age 62.8 (SD 8.4) female:male 914:1182 **Inclusion criteria** 1. Male or female participants $\geq$ 40 years of age and < 80 at visit 1 2. Established clinical history of COPD as defined by ATS/ERS 3. Current or former smokers with a history of at least 10 pack-years of cigarette smoking. 4. Average of the -60 and the -30 min pre-dose FEV1 assessments must be < 80% predicted normal value calculated using NHANES 3 reference equations 5. Willing and, in the opinion of the investigator, able to adjust current COPD therapy as required by the protocol **Exclusion criteria** 1. Significant diseases other than COPD, i.e. disease or condition which, in the opinion of the investigator, may put the participant at risk because of participation in the study or may influence either the results of the study or the participant's ability to participate in the study

	2. Current diagnosis of asthma or alpha-1 antitrypsin deficiency 3. Other active pulmonary disease such as active TB, lung cancer, bronchiectasis, sarcoidosis, idiopathic interstitial pulmonary fibrosis, primary pulmonary hypertension, or uncontrolled sleep apnoea 4. Hospitalised due to poorly controlled COPD within 3 months prior to screening or during the screening period 5. Poorly controlled COPD, defined as acute worsening of COPD that requires treatment with OCS or antibiotics within 6 weeks prior to screening or during the screening period 6. Lower respiratory tract infections that required antibiotics within 6 weeks prior to screening or during the screening period 7. Unstable ischaemic heart disease, left ventricular failure, or documented MI within 12 months of enrolment 8. Recent history of acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass graft within the past 3 months 9. Congestive heart failure NYHA Class 3/4) 10. Clinically significant abnormal 12-lead ECG 11. Abnormal liver function tests defined as AST, ALT, or total bilirubin $\geq$ 1.5 times ULN at visit 1 and on repeat testing 12. Cancer not in complete remission for at least 5 years 13. History of hypersensitivity to β2-agonists, glycopyrronium or other muscarinic anticholinergics, lactose/milk protein or any component of the MDI
Interventions	**Inhaler device** 1. Glycopyrronium/formoterol: MDI 2. Glycopyrronium: MDI 3. Fluticasone furorate: MDI 4. Open-label tiotropium: bromide inhalation powder 5. Placebo: MDI **Allowed co-medications:** rescue albuterol, ICS, PDE4 inhibitor
Outcomes	**Primary:** CFB in morning pre-dose trough FEV1 at week 24 (time frame: baseline and at week 24)
Notes	**Funding:** Pearl Therapeutics **Identifiers:** NCT01854645

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Tiotropium was open-label

Martinez 2017a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Tiotropium was open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout relatively high and uneven among active comparators (glycopyrronium/formoterol 18.6%, glycopyrronium 23.5%, fluticasone furorate 18.1%, tiotropium 13.7%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Martinez 2017b

Methods	**Design:** randomised, double-blind, chronic-dosing, placebo-controlled, parallel-group, multi centre study **Duration:** 24 weeks **Location:** USA
Participants	**Population** 1. Glycopyrronium/formoterol 14.4/9.6 μg (510) 2. Glycopyrronium 14.4 μg (439) 3. Formoterol 9.6 μg (438) **Baseline characteristics:** age 62.9 (SD 8.3) female:male 723:886 **Inclusion criteria** 1. Male or female, $\geq$ 40 years of age and < 80 at visit 1 2. Established clinical history of COPD as defined by the ATS/ERS 3. Current or former smokers with a history of at least 10 pack-years of cigarette smoking 4. FEV1/FVC ratio of < 0.70 and FEV1 < 80% predicted normal and $\geq$ 750 mL if FEV1 < 30% of predicted normal value 5. Willing and, in the opinion of the investigator, able to adjust current COPD therapy as required by the protocol **Exclusion criteria** 1. Significant diseases other than COPD, i.e. disease or condition which, in the opinion of the investigator, may put the participant at risk because of participation in the study or may influence either the results of the study or the participant's ability to participate in the study 2. Current diagnosis of asthma or alpha-1 antitrypsin deficiency 3. Other active pulmonary disease such as active TB, lung cancer, bronchiectasis, sarcoidosis, idiopathic interstitial pulmonary fibrosis, primary pulmonary hypertension, or uncontrolled sleep apnoea 4. Hospitalised due to poorly controlled COPD within 3 months prior to screening or during the screening period 5. Poorly controlled COPD, defined as acute worsening of COPD that requires treatment with OCS or antibiotics within 6 weeks prior to screening or during the screening period

	6. Lower respiratory tract infections that required antibiotics within 6 weeks prior to screening or during the screening period 7. Unstable ischaemic heart disease, left ventricular failure, or documented MI within 12 months of enrolment 8. Recent history of acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass graft within the past 3 months 9. Congestive heart failure (NYHA Class 3/4) 10. Clinically significant abnormal 12-lead ECG 11. Abnormal liver function tests defined as AST, ALT, or total bilirubin $\geq$ 1.5 times ULN at visit 1 and on repeat testing 12. Cancer not in complete remission for at least 5 years 13. History of hypersensitivity to β2-agonists, glycopyrronium or other muscarinic anticholinergics, lactose/milk protein or any component of the MDI
Interventions	**Inhaler device:** 1. Glycopyrronium/formoterol: MDI 2. Glycopyrronium: MDI 3. Fluticasone furorate: MDI 4. Open-label tiotropium: bromide inhalation powder 5. Placebo: MDI **Allowed co-medications:** rescue albuterol, ICS, PDE4 inhibitor
Outcomes	**Primary:** CFB in morning pre-dose trough FEV1
Notes	**Funding:** Pearl Therapeutics **Identifiers:** NCT01854658

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout relatively high and uneven among active comparators (glycopyrronium/formoterol 21.2%, glycopyrronium 17.0%, fluticasone furorate 15.6%, tiotropium 26.3%)

Martinez 2017b (*Continued)*

Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

NCT00876694 2011

Methods	**Design:** multicentre, randomised, open-label, parallel-group study **Duration:** 52 weeks **Location:** Japan
Participants	**Population** 1. Indacaterol 300 μg (125) 2. Salmeterol 50 μg (61) **Baseline characteristics:** age 69.1 (SD 7.97) female:male 10:176 **Inclusion criteria** 1. Diagnosis of COPD (moderate-to-severe as classified by the GOLD criteria) 2. Smoking history of at least 20 pack-years 3. Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value 4. Post-bronchodilator FEV1/FVC (forced vital capacity) < 70% **Exclusion criteria:** a COPD exacerbation in the 6 weeks prior to visit 1 or during the run-in period, concomitant pulmonary disease, asthma, diabetes type 1 or uncontrolled diabetes type 2, lung cancer or a history of lung cancer, certain cardiovascular comorbid conditions
Interventions	**Inhaler device** 1. Indacaterol 300 µg once daily via DPI 2. Salmeterol 50 µg twice daily via Diskus **Allowed co-medications:** salbutamol as rescue
Outcomes	Long-term safety and tolerability (particularly with regard to ECG, laboratory tests, vital signs and AEs) of indacaterol
Notes	**Funding:** Novartis **Identifiers:** NCT00876694 2011, CQAB149B1303

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label

NCT00876694 2011 (*Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was relatively low and even between two groups (16.8% in indacaterol, 19.7% in salmeterol group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

NCT01536262 2014

Methods	**Design:** randomised, double-blind, parallel-group study **Duration:** 52 weeks **Location:** Japan, multicentre
Participants	**Population** 1. Olodaterol 5 μg (41) 2. Tiotropium + olodaterol 2.5/5 μg (40) 3. Tiotropium + olodaterol 5/5 μg (41) **Baseline characteristics:** age 69.9 (SD 7.3), F:M 5:117 **Inclusion criteria** 1. Diagnosis of COPD 2. Relatively stable airway obstruction with post FEV1 < 80% predicted normal and post FEV1/FVC < 70% 3. Male or female Japanese patients, $\geq$ 40 years of age 4. Smoking history of > 10 pack-years. **Exclusion criteria** 1. Significant disease other than COPD 2. Clinically relevant abnormal lab values 3. History of asthma 4. Significant comorbidities 5. Known active TB 6. Malignancy treated by resection, radiation therapy or chemotherapy within last 5 years 7. Other pulmonary diseases 8. Regular use of daytime oxygen therapy for > 1 h/d 9. Pregnant or nursing women 10. Women of childbearing potential not using a highly effective method of birth control 11. Narrow-angle glaucoma or micturition disorder due to prostatic hyperplasia
Interventions	**Inhaler device** 1. Tiotropium + olodaterol FDC once-daily inhalation: Respimat 2. Olodaterol once daily inhalation: Respimat 3. Tiotropium and Olodaterol FDC once-daily inhalation: Respimat **Allowed co-medications:**

NCT01536262 2014 (*Continued*)

Outcomes	**Primary:** number (%) of participants with drug-related AEs
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01536262 2014, 1237.22

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was high with olodaterol 5 µg (19.5%) uneven compared with tiotropium/olodaterol 5/5 µg (4.9%). Analysed using treated set: this participant set included all participants who received at least 1 dose of treatment. Imputaion method not described
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Ohar 2014

Methods	**Design**: randomised, parallel-group study **Duration**: 26 weeks **Location**: 103 centres in Argentina, Norway and USA
Participants	**Population** 1. Fluticasone propionate/salmeterol 250/50 µg (314) 2. Salmeterol 50 µg (325) **Baseline characteristics:** age 62.9 (SD 9.22) female:male 291:348 **Inclusion criteria**: > 40 years of age and a historical FEV1/FVC < 0.7, recent event (within 14 days of randomisation) of: < 10-day hospitalisation for an acute COPD exacerbation, or exacerbation requiring treatment with OCS or OCS + antibiotics in an ER, or during a physician's office visit. If the index event was office-based, a 6-month history of hospitalisations attributed to acute exacerbation of COPD was also required

	Exclusion criteria: diagnosis of pneumonia, congestive heart failure, or other complicating comorbidities, previous lung resection surgery (e.g. lobectomy and pneumonectomy) within the year preceding visit 1 (screening, asthma as primary diagnosis), lung cancer, cystic fibrosis, pulmonary fibrosis, active TB, or sarcoidosis, clinically significant cardiac arrhythmias, current malignancy or a previous history of cancer in remission for < 5 years (localised basal cell or squamous cell carcinoma of the skin that had been resected was not excluded), pregnancy, hypersensitivity to any beta-agonist, sympathomimetic drug, or corticosteroid
Interventions	1. Salmeterol 50 µg twice daily (LABA) 2. Salmeterol/fluticasone 50/250 µg twice daily (LABA/ICS) **Inhaler device:** Diskus dry powder **Allowed co-medications:** albuterol as needed. Tiotropium
Outcomes	Pre-dose FEV1, exacerbation outcomes
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01110200, ADC113874

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Allocation concealment (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No details provided but outcomes not subject to detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates were high (fluticasone propionate/salmeterol 22.7%, salmeterol 25.7%) but the reasons for dropout were similar between two groups. ITT population with endpoint analysis was used for miss-

Ohar 2014 (*Continued*)

		ing data and premature withdrawal
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the results summary on clinicaltrials.gov

Pepin 2014

Methods	**Design:** multicentre, randomised, double-blind, parallel-group, chronic-dosing, active- and placebo-controlled study **Duration:** 12 weeks **Location:** Argentina, France, Germany, Italy, Norway, Russian Federation, Ukraine
Participants	**Population** 1. Fluticasone furorate/vilanterol 100/25 μg (127) 2. Tiotropium 18 μg (130) **Baseline characteristics:** age 67.3 (7.28) female:male 37/220 **Inclusion criteria** 1. Outpatients 2. Signed and dated written informed consent to participate 3. Male or female participants 4. $\geq$ 40 years of age at screening (visit 1) 5. Clinical history of COPD in accordance with ATS/ERS definition 6. Current or prior history of $\geq$ 10 pack-years of cigarette smoking at screening (visit 1) 7. Measured post-albuterol/salbutamol FEV1 < 70% of predicted at screening (visit 1) 8. Measured post-albuterol/salbutamol FEV1/FVC ratio of $\leq$ 0.70 at screening (visit 1) 9. Hospitalised or treated with OCS or antibiotics for their COPD within the last 3 years prior to screening (visit 1) **Exclusion criteria:** BMI of $\leq$ to 35
Interventions	**Inhaler device** 1. Fluticasone furoate (GW685698)/vilanterol (GW642444) 100/25 μg: Novel DPI 2. Tiotropium (18 μg) administered once daily via a HandiHaler **Allowed co-medications:** salbutamol/albuterol as needed
Outcomes	**Primary:** mean CFB in aortic pulse wave velocity at the end of the 12-week treatment period (day 84)
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01395888, HZC115247

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Interactive voice-response system
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator and treating physician were kept blinded unless a medical emergency or a serious adverse medical condition arose
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was low and even between two groups (11.8% in fluticasone furorate/vilanterol and 13.1% in tiotropium group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Perng 2009

Methods	**Design:** randomised (not double-blinded) clinical trial **Duration:** 12 weeks **Location:** Taiwan
Participants	**Population** 1. Salmeterol/fluticasone propionate 500/50 μg (33) 2. Tiotropium 18 μg (34) **Baseline characteristics:** age 73.2. female:male 4/63 **Inclusion criteria:** clinical diagnosis of COPD**,** aged 40-85 years; were a current or former smoker (history 20 pack-years); had a post-bronchodilator FEV1 $\leq$ 80% of the predicted value and FEV1/FVC < 70% **Exclusion criteria:** no history of asthma, atopy (as defined by a positive reaction to one or more allergen in a fluoroenzyme immunoassay) or any other active lung disease. Participants were either newly diagnosed or had not taken corticosteroids (either oral or inhaled), or any other bronchodilators or theophylline, for a minimum of 3 months prior to the commencement of the study
Interventions	**Inhaler device** 1. Salmeterol/fluticasone propionate 25/250 μg Evohaler (GlaxoSmithKline) 2. Tiotropium 18 μg HandiHaler (Boehringer Ingelheim) **Allowed co-medications:** not described
Outcomes	Pulmonary function, serum C reactive protein, sputum induction and assessment of health-related QoL

Perng 2009 (*Continued)*

Notes	**Funding:** None reported **Identifiers:** none	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a computer-generated list of random numbers
Allocation concealment (selection bias)	Low risk	Randomisation was performed using a computer-generated list of random numbers
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was low and relatively even between 2 groups (10% in salmeterol/fluticasone propionate and 14.7 % in tiotropium group)
Selective reporting (reporting bias)	Unclear risk	Unable to locate protocol to check outcome reporting

RADIATE 2016

Methods	**Design:** multicentre, randomised, double-blind, parallel-group, placebo- and active-controlled study **Duration:** 52 weeks **Location:** Belgium, Bulgaria, Greece, Hungary, Ireland, Russian Federation, Slovakia, Spain, Turkey, UK
Participants	**Population** 1. Indacaterol/glycopyrronium 110/50 μg (407) 2. Tiotropium 18 μg (405) **Baseline characteristics:** age 64.5 (SD 8.14) female:male 318:898 **Inclusion criteria** 1. Male and female adults aged ≥ 40 years 2. Stable COPD according to GOLD 2011 strategy 3. Airflow limitation indicated by a post-bronchodilator FEV1 ≥ 30% and < 80% of the predicted normal, and a post-bronchodilator FEV1/FVC < 0.70

	4. Current or ex-smokers with a smoking history of at least 10 pack-years 5. mMRC ≥ grade 2 **Exclusion criteria** 1. History of long QT syndrome or prolonged QTc 2. COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalisation in the 6 weeks prior to visit 1 3. Type I or uncontrolled type 2 diabetes 4. History of asthma or have concomitant pulmonary disease 5. Paroxysmal (e.g. intermittent) atrial fibrillation. Only patients with persistent atrial fibrillation and controlled with a rate control strategy for at least six months could be eligible. 6. Clinically significant renal, cardiovascular, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities that could interfere with the assessment of safety
Interventions	**Inhaler device** 1. Indacaterol/glycopyrronium (QVA149) 110/50 μg Novartis Concept1 DPI 2. Tiotropium 18 μg HandiHaler DPI **Allowed co-medications:** rescue albuterol
Outcomes	**Primary:** number of patients with serious AEs
Notes	**Funding:** Novartis **Identifiers:** NCT01610037, CQVA149A2339

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively low in both included groups (tiotropium 12.6%, indacaterol/glycopyrronium 14.5%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Rennard 2009

Methods	**Design**: randomised, double-blind, double-dummy, parallel-group, active- and placebo-controlled, multicentre study **Duration**: 52 weeks (+ 2-week run-in period) **Location**: 237 sites in the USA, Europe and Mexico
Participants	**Population**: 1964 participants were randomised to 1. formoterol (495) 2. formoterol/budesonide at two doses (494 and 494) 3. placebo (481) **Baseline characteristics** Age (mean years): formoterol 62.9, formoterol/budesonide (9/320 µg) 63.2, formoterol/budesonide (9/160 µg) 63.6, placebo 62.9 % male: formoterol 65.3, formoterol/budesonide (9/320 µg) 62.3, formoterol/budesonide (9/160 µg) 62.8, placebo 65.3 % FEV1 predicted: formoterol 39.3, formoterol/budesonide (9/320 µg) 38.6, formoterol/budesonide (9/160 µg) 39.6, placebo 40.8 Pack-years (median): formoterol 40, formoterol/budesonide (9/320 µg) 40, formoterol/budesonide (9/160 µg) 40, placebo 40 **Inclusion criteria**: men and women aged ≥ 40 years; moderate-severe COPD for > 2 years; history of at least 10 pack-years **Exclusion criteria**: history of asthma or seasonal rhinitis before age 40; significant/unstable cardiovascular disorder; significant respiratory tract disorder other than COPD; homozygous alpha1-antitrypsin deficiency or other clinically significant comorbidities precluding participation
Interventions	1. Formoterol 12 µg twice daily (LABA) 2. Formoterol/budesonide 9/320 µg (LABA/ICS) 3. Formoterol/budesonide 9/160 µg (LABA/ICS) 4. Placebo **Inhaler device:** DPI **Allowed co-medications:** salbutamol was allowed as relief medication. Previous ICSs were discontinued, and disallowed medication included long-acting anticholinergics; inhaled LABAs or SABAs (other than salbutamol); oral beta-adrenoreceptor agonists; ephedrine; leukotriene receptor agonists; xanthine derivatives except for short-term use
Outcomes	SGRQ, COPD exacerbations, pre-dose FEV1, 1 h post-dose FEV1, morning and evening PEF
Notes	**Funding**: AstraZeneca **Identifier(s)**: NCT00206167

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, parallel-group study (no specific details, industry sponsored)
Allocation concealment (selection bias)	Unclear risk	No details provided

Rennard 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	To maintain blinding, participants received both a pressurised MDI and a DPI containing either active treatment or double-dummy placebo as appropriate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Included outcomes unlikely to be affected by detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rate was high (budesonide/formoterol 320/9 μg 27.1%, budesonide/formoterol 160/9 μg 28.9%, formoterol 31.7%) but the reasons for withdrawal were similar across the groups
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published report

Rheault 2016

Methods	**Design:** multicentre, randomised, open-label, 2-arm, parallel-group study **Duration:** 12 weeks **Location:** Argentina, Chile, Czechia, Germany, Hungary, Norway, Romania, Russian Federation, Spain, Sweden
Participants	**Population** 1. Umeclidinium 62.5 μg (516) 2. Glycopyrronium 44 μg (518) **Baseline characteristics:** age 64.01 (SD 8.3) female:male 329:705 **Inclusion criteria** 1. Outpatient 2. Signed and dated written informed consent prior to study participation 3. $\geq$ 40 years at visit 1 4. Male and female participants 5. Women of: i) non-child-bearing potential i.e. physiologically incapable of becoming pregnant, including any women who is post-menopausal or surgically sterile. Surgically sterile women are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation. Post-menopausal women are defined as being amenorrhoeic for > 1 year with an appropriate clinical profile, e.g. age appropriate, > 45 years, in the absence of hormone replacement therapy ii) child-bearing potential, with negative pregnancy test at screening, and agrees to use one of the acceptable contraceptive methods consistently and correctly i.e. in accordance with the approved product label and the instructions of the physician for the duration of the study - screening to follow-up contact 6. Established clinical history of COPD in accordance with the definition by the ATS/ERS

	7. Current or former cigarette smokers with a history of cigarette smoking of ≥ 10 pack-years (number of pack-years = (number of cigarettes per day / 20) x number of years smoked (e.g. 20 cigarettes/day for 10 years, or 10 cigarettes/day for 20 years both equal 10 pack-years)). Former smokers are defined as those who have stopped smoking for at least 6 months prior to visit 1. Pipe and/or cigar use cannot be used to calculate pack-year history 8. Pre and post-albuterol/salbutamol FEV1/FVC ratio of < 0.70 and a post-albuterol/salbutamol FEV1 of ≥ 30% and ≤ 70% of predicted normal values at visit 1. Predicted values will be based upon the ERS Global Lung Function Initiative 9. A score of ≥2 on the modified mMRC at visit 1 **Exclusion criteria** 1. Current diagnosis of asthma 2. Other respiratory disorders: known alpha-1 antitrypsin deficiency, active lung infections (such as TB), and lung cancer. Any other significant respiratory conditions 3. Participants considered unlikely to survive the duration of the study period or with any rapidly progressing disease or immediate life-threatening illness (e.g. cancer). In addition, any participant with any condition (e.g. neurological condition) that is likely to affect respiratory function 4. Unstable or life threatening cardiac disease: LAMA should be used with caution in participants with severe CVD. In the opinion of the investigator, use should only be considered if the benefit is likely to outweigh the risk in conditions such as: MI or unstable angina in the last 6 months, unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months, NYHA Class 4 heart failure 5. Antimuscarinic effects: participants with medical conditions such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy, or bladder neck obstruction should only be included if, in the opinion of the study physician, the benefit outweighs the risk 6. Hospitalisation for COPD or pneumonia within 12 weeks prior to visit 1 7. Lung volume reduction surgery within the 12 months prior to visit 1 8. Abnormal findings based on 12-Lead ECG: e.g. atrial fibrillation with rapid ventricular rate > 120 bpm; sustained or nonsustained ventricular tachycardia; second degree heart block Mobitz type 2 or third degree heart block (unless pacemaker or defibrillator had been inserted) 9. Inability to withhold albuterol/salbutamol for the 4-h period required prior to spirometry testing at each study visit 10. LTOT, described as oxygen therapy prescribed for greater than 12 h/d. As-needed oxygen use (i.e. ≤ 12 h/d) is not exclusionary. 11. Regular use (prescribed for use every day, not for as-needed use) of short-acting bronchodilators (e.g. albuterol/salbutamol) via nebulised therapy 12. Known or suspected history of alcohol or drug abuse within 2 years prior to visit 1
Interventions	**Inhaler device:** Umeclidinium 62.5 μg DPI Glycopyrronium bromide as inhalation capsules, 44 μg per capsule, BREEZHALER inhalers **Allowed co-medications:** ICSs. albuterol/salbutamol for as-needed rescue medication
Outcomes	**Primary:** CFB in trough FEV1 on day 85

Rheault 2016 *(Continued)*

Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT02236611, 201315 (GSK)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Allocation concealment (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was low in both included groups (umeclidinium 5.0%, glycopyrronium 6.6%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Rossi 2014

Methods	**Design**: randomised, double-blind, parallel-group study **Duration**: 26 weeks. **Location**: Argentina, Colombia, Italy, Malaysia, Mexico, Netherlands, Spain, Switzerland, UK
Participants	**Population** 1. Fluticasone propionate/salmeterol 500/50 μg (288) 2. Salmeterol 50 μg (293) **Baseline characteristics:** age 66.0 (SD 8.49) female:male 180:401 **Inclusion criteria**

	1. Moderate COPD (stage 2) 2. Able to perform spirometry assessments 3. Current or ex-smokers 4. On treatment with the FDC of salmeterol 50 µg/fluticasone propionate 500 µg DPI twice daily for the treatment of COPD for ≥ 3 months directly preceding visit 1 **Exclusion criteria** 1. Having had a COPD exacerbation that required treatment with antibiotics and/or OCS and/or hospitalisation in the past year 2. History of, or current ECG abnormality 3. Asthma
Interventions	**Inhaler device:** 1. Indacaterol DPI 2. Salmeterol/fluticasone DPI **Allowed co-medications:** salbutamol as rescue
Outcomes	**Primary:** trough FEV1 at 12 weeks (imputed by using the last observation carried forward method)
Notes	**Funding:** Novartis **Identifiers:** NCT01555138, CQAB149B2401

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants, investigator staff, personnel performing assessments and data analysts was maintained by ensuring randomisation data remained strictly confidential and inaccessible to anyone involved in the study until the time of unblinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively low in both included groups (indacaterol 16.0%, salmeterol/fluticasone propionate 13.2%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Sarac 2016

Methods	**Design:** an open, prospective, randomised trial **Duration:** 52 weeks **Location:** Turkey
Participants	**Population** 1. Futicasone propionate/salmeterol 500/50 μg (22) 2. Tiotropium 18 μg (22) **Baseline characteristics:** age 66.6 female:male 2/42 **Inclusion criteria:** 35-80 years old, they had a smoking history of 10 pack-years or more, their FEV1 level was between 50% and 80% and they reported at least one exacerbation in the preceding year **Exclusion criteria:** a prior diagnosis of asthma, previous documentation of bronchial hyperreactivity, history of allergy and/or atopy, presence of congestive heart failure or any other cardiopulmonary disease that might interfere with the participant's follow-up
Interventions	**Inhaler device** 1. Salmeterol 50 μg/fluticasone 500 μg combination as DPI (Diskus) 2. Tiotropium DPI (HandiHaler) **Allowed co-medications:** short-acting bronchodilators as needed
Outcomes	COPD exacerbations, CAT score, 6MWD, AEs
Notes	**Funding:** none reported **Identifiers:** none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear how many dropped out
Selective reporting (reporting bias)	Unclear risk	Could not locate protocol to check outcome reporting

SCO100470 2006

Methods	**Design**: multicentre, randomised, double-blind, double dummy, parallel-group design **Duration**: 6 months (+ run-in of unclear duration) **Location**: conducted at 135 centres in 20 countries
Participants	**Population**: 1050 people were randomised to 1. fluticasone (532) 2. fluticasone/salmeterol combination (518) **Baseline characteristics** Age (mean years): salmeterol 63.7, fluticasone/salmeterol 63.5 % male: salmeterol 77.3, fluticasone/salmeterol 78.4 % FEV1 predicted: not reported Pack-years (mean): not reported **Inclusion criteria**: Male or female, aged 40-80 years with an established history of GOLD stage 2 COPD; poor reversibility of airflow obstruction (defined as ≤ 10% increase in FEV1 as a percentage of the normal predicted value); a minimum score of 2 on the mMRC Scale, and a smoking history of > 10 pack-years. In addition, participants had to achieve a composite symptom score of 120 (out of 400 maximum score, measured using visual analogue scales) on at least 4 of the last 7 days of the run-in period, and to have a BDI score of 7 units at visit 2 **Exclusion criteria**: asthma or atopic disease, lung disease likely to confound the drug response other than COPD, recent exacerbation (within 4 weeks or screening or during run-in); LTOT or pulmonary rehabilitation or had taken tiotropium bromide, ICSs or anti-leukotriene medication within 14 days of visit 1
Interventions	1. Salmeterol 50 µg twice daily (LABA) 2. Salmeterol/fluticasone 50/500 µg twice daily (LABA/ICS) **Inhaler device**: Diskus accuhaler **Allowed co-medications**: not reported
Outcomes	TDI, CFB in trough FEV1, CFB in trough FVC and FVC/FEV1 ratio, TDI focal score, CFB in post-dose FEV1, FVC and FVC/FEV1 ratio, CFB in mean morning PEF, CFB in SGRQ
Notes	**Funding**: GlaxoSmithKline **Identifier(s)**: SCO100470 (GSK)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to treatment via an interactive voice-response system
Allocation concealment (selection bias)	Low risk	Participants were randomised to treatment via an interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind (participants and personnel/investigators)

SCO100470 2006 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded (presumed investigators were also outcomes assessors)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout low and even between groups (11.4% vs 13.9%). The ITT population (all participants randomised and confirmed as having received at least 1 dose of double-blind study medication), was the primary population for analysis of all efficacy and health outcomes variables; the safety population (identical to the ITT population), was used for analysis of all safety variables
Selective reporting (reporting bias)	Low risk	All stated outcomes were reported and no expected outcomes were missing

SCO40034 2005

Methods	**Design:** randomised, double-blind, double-dummy, multicentre, parallel-group exploratory study **Duration:** 12 weeks **Location:** 17 centres in the Netherlands
Participants	**Population:** 125 adults with a clinical history of moderate-severe COPD 1. Fluticasone 500 μg + salmeterol 50 μg twice daily + placebo 2. Tiotropium 18 μg once daily + placebo to match fluticasone + salmeterol **Baseline characteristics:** age mean 63.7 (fluticasone/salmeterol) 65.3 (tiotropium) female:male 18:43 (fluticasone/salmeterol), 14:50 (tiotropium), white 100% **Inclusion criteria:** aged 40-80 years inclusive. Post-bronchodilator FEV1 < 70% of predicted normal. Participants must have had a smoking history (current or former smokers) of > 10 pack-years **Exclusion criteria:** within 4 weeks prior to visit 1; COPD exacerbation; received oral, parenteral or depot corticosteroids for a COPD exacerbation; received antibiotic therapy and/or been hospitalised for either a lower respiratory tract infection or for COPD exacerbation, or had any changes in their COPD medication
Interventions	**Inhaler device** 1. Combination of fluticasone 500 μg and salmeterol 50 μg twice daily via Diskus inhaler + placebo capsules to match tiotropium delivered once daily via the HandiHaler inhaler 2. Tiotropium 18 μg once daily via HandiHaler + placebo to match FPS Diskus combination product delivered twice daily **Allowed co-medications:** albuterol as rescue
Outcomes	Since this study was primarily an exploratory study to compare the effect of fluticasone/salmeterol with tiotropium on clinical efficacy, a primary endpoint was not identified

Notes	**Funding:** GlaxoSmithKline **Identifiers:** SCO40034 (GSK)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Allocation concealment (selection bias)	Low risk	A validated computerised system (RandAll; GlaxoSmithKline, UK) - using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Someone who was not directly involved in the study received and documented all returned medication in a drug accountability log. A separate accountability log was maintained for each participant and participants administered their own study medication without the investigator or site personnel being present. Participants were unblinded only when knowledge of the treatment was essential for the clinical management or welfare of the participant. Cases of unblinding were to be reported and documented immediately
Incomplete outcome data (attrition bias) All outcomes	High risk	117/125 (94%) completed the study, but withdrawals were imbalanced with 1 (2%) from the fluticasone/salmeterol arm and 7 (11%) from the tiotropium arm
Selective reporting (reporting bias)	High risk	Uable to locate protocol. Clinical study report not available through GlaxoSmithKline

SCO40041 2008

Methods	**Design**: randomised, double-blind parallel-group trial **Duration**: 3 years **Location**: 31 centres in the USA
Participants	**Population**: 186 people were randomised to 1. Salmeterol 50 µg twice daily (94) 2. Fluticasone/salmeterol combination 50/250 µg twice daily (92) **Baseline characteristics** Age (mean years): salmeterol 65.9, fluticasone/salmeterol 65.4 % male: salmeterol 62.8, fluticasone/salmeterol 59.8 % FEV1 predicted: not reported Pack-years (mean): not reported **Inclusion criteria**: male/female participants with an established clinical history of COPD (including a history of exacerbations), a baseline (pre-bronchodilator) FEV1 < 70% of the predicted normal value, a baseline (pre-bronchodilator) FEV1/FVC ratio 70%, have at least one evaluable native hip and have a smoking history of 10 pack-years **Exclusion criteria**: history of or evidence for metabolic bone diseases other than osteoporosis or osteopenia. Asthma, chronic lung disease other than COPD. LTOT > 12 h/d. Chronic steroid use
Interventions	1. Salmeterol 50 µg twice daily (LABA) 2. Salmeterol/fluticasone 50/250 µg twice daily (LABA/ICS) **Inhaler device:** Diskus **Allowed co-medications:** albuterol/salbutamol, theophyllines, short- and long-acting anti-cholinergic agents, Combivent
Outcomes	Change in bone mineral density at the lumbar spine and hip, AEs, SAEs, fatal SAEs
Notes	**Funding**: GlaxoSmithKline **Identifier(s)**: NCT00355342, GSK SCO40041

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised to treatment via an interactive voice-response system
Allocation concealment (selection bias)	Low risk	Participants were randomised to treatment via an interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind (participants and personnel/investigators)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind (participants and personnel/investigators)

SCO40041 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal was very high in both groups (39% and 41%) but breakdown for withdrawals was similar between two groups
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all outcomes were reported in the GSK clinical study report

Sharafkhaneh 2012

Methods	**Design**: randomised, double-blind, double-dummy, parallel-group, multicentre study **Duration**: 12 months (+ 2 week run-in) **Location**: 180 study sites in the USA, Central and South America, and South Africa
Participants	**Population**: 1219 participants were randomised to 1. formoterol (404) 2. formoterol/budesonide combination, 2 doses (407 and 408) **Baseline characteristics** Age (mean years): formoterol 62.5, formoterol/budesonide (9/320) 63.8, formoterol/budesonide1 60 62.8 % male: formoterol 56.8, formoterol/budesonide (9/320) 64.4, formoterol/budesonide (9/160) 64.7 % FEV1 predicted: formoterol 37.5, formoterol/budesonide (9/320) 37.9, formoterol/budesonide (9/160) 37.6 Pack-years (mean): formoterol 43, formoterol/budesonide (9/320) 46, formoterol/budesonide (9/160) 44 **Inclusion criteria**: current or ex-smokers with a smoking history of 10 pack-years, aged $\geq$ 40 years, with a clinical diagnosis of COPD with symptoms for > 2 years. Participants were required to have a history of 1 COPD exacerbation requiring treatment with a course of systemic corticosteroids, antibiotics, or both, within 12 months before screening (visit 1) and documented use of an inhaled short-acting bronchodilator as rescue medication. At screening, a pre-bronchodilator FEV1 of 50% of predicted normal and a pre-bronchodilator FEV1/FVC of < 70% also were required **Exclusion criteria**: current, previous (within past 60 days), or planned enrolment in a COPD pulmonary rehabilitation programme, treatment with OCS, and incidence of a COPD exacerbation or any other significant medical diagnosis between the screening and randomisation visits
Interventions	1. Formoterol 9 μg twice daily (LABA) 2. Formoterol/budesonide 9/320 μg twice daily (LABA/ICS) 3. Formoterol/budesonide 9/160 μg twice daily (LABA/ICS) **Inhaler device**: 1, DPI; 2 and 3 pressurised metered dose **Allowed co-medications**: albuterol pressurized MDI 90 µg 2 inhalations was provided for as-needed use during screening and run-in, and throughout the study
Outcomes	COPD exacerbations, FEV1, FVC, morning and evening PEF, diary card symptoms, rescue medication use, BODE index, exercise capacity, health-related QoL (SGRQ), AEs

Notes	**Funding**: AstraZeneca **Identifier(s)**: NCT00419744, D589CC00003 (AstraZeneca)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignments were made sequentially by interactive voice-response system following a computer-generated allocation schedule produced in advance
Allocation concealment (selection bias)	Low risk	Assignments were made sequentially by interactive voice-response system following a computer-generated allocation schedule produced in advance
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To maintain participant and investigator blinding, all active treatments were provided in blinded treatment kits. Participants in the budesonide/formoterol pMDI groups received a placebo DPI and those in the formoterol DPI group received a placebo pMDI
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded (presumed investigators were also outcomes assessors)
Incomplete outcome data (attrition bias) All outcomes	High risk	The withdrawal rates were high and relatively uneven (budesonide/formoterol 320/9 μg 28.7% budesonide/formoterol 160/9 μg 28.9%, formoterol 9 μg 32.9%), especially compared to the low event rates for the outcomes of interest
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported in detail.

Singh 2014

Methods	**Design:** double-blind, parallel-group, active- and placebo-controlled, multicentre phase 3 study **Duration:** 24 weeks **Location:** Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Republic of Korea, Netherlands, Poland, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Ukraine, UK
Participants	**Population** 1. Aclidinium/formoterol 400/12 μg (385) 2. Aclidinium 400 μg (385) 3. Formoterol 12 μg (384) **Baseline characteristics:** age 63.2 (SD 8.0), female:male 560:1169 **Inclusion criteria** 1. Adult men or non-pregnant, non-lactating women aged $\geq$ 40. 2. Current or ex-cigarette smoker, with a smoking history of at least 10 pack-years 3. Clinical diagnosis of stable COPD according to the GOLD criteria at the screening visit 4. FEV1/FVC at the screening visit measured between 10-15 min post-inhalation of 400 μg of salbutamol is < 70% (i.e. 100 x post-salbutamol FEV1 /FVC < 70%) 5. Diagnosis of moderate-severe COPD according to the GOLD classification (stages 2 and 3) at the screening visit: FEV1 measured between 10-15 min post-inhalation of 400 μg of salbutamol is 30% < FEV1 < 80% of the predicted normal value (i.e. 100 x post-salbutamol FEV1/predicted FEV1 must be < 80% and $\geq$ 30%) **Exclusion criteria:** 1. History or current diagnosis of asthma 2. Any respiratory tract infection (including the upper respiratory tract) or COPD exacerbation in the 6 weeks before screening visit 3. Hospitalised for COPD exacerbation within 3 months prior to screening visit 4. Clinically significant respiratory conditions defined as: known active TB; history of interstitial lung or massive pulmonary thromboembolic disease; pulmonary resection or lung volume reduction surgery within 12 months prior to screening visit; history of lung transplantation; history of bronchiectasis secondary to respiratory diseases other than COPD (e.g. cystic fibrosis and Kartagener's syndrom); known a1-antitrypsin deficiency 5. Use of LTOT ($\geq$ 15 h/d) 6. Clinically significant cardiovascular conditions defined as: MI within the 6 months prior to screening; thoracic surgery within 12 months prior to screening; unstable angina or unstable arrhythmia which had required changes in the pharmacological therapy or other intervention within 12 months prior to screening, or newly diagnosed arrhythmia within the previous 3 months prior to screening; hospitalisation within 12 months prior to screening for heart failure functional classes 3 (marked limitation of activity and only comfortable at rest) and 4 (need of complete rest, confinement to bed or chair, discomfort at any physical activity and presence of symptoms at rest) as per the NYHA 7. Interval corrected for heart rate "QTc" (calculated according to formulae (QTc = QT/RR1/2) > 470 msec as indicated in the centralised reading report assessed at screening visit 8. Clinically relevant abnormalities in the clinical laboratory tests, ECG parameters or in the physical examination at screening, if the abnormality defined a disease state

	listed as exclusion criteria, except for those related to COPD 9. Known narrow-angle glaucoma, symptomatic bladder neck obstruction or acute urinary retention. 10. Symptomatic non-stable prostate hypertrophy. (However, patients with well-controlled, stable, asymptomatic benign prostatic hypertrophy were not excluded). 11. Known uncontrolled history of infection with HIV and/or active hepatitis 12. Current diagnosis of cancer other than basal or squamous cell skin cancer 13. Life expectancy of < 1 year
Interventions	**Inhaler device** 1. Breath-actuated, multiple-dose DPI 2. Aclidinium Bromide/Formoterol Fumarate 3. Aclidinium Bromide 4. Formoterol Fumarate **Allowed co-medications:** as-needed salbutamol**,** ICSs
Outcomes	**Primary:** CFB in 1-h morning post-dose FEV1, CFB in morning pre-dose (trough) FEV1
Notes	**Funding:** AstraZeneca **Identifiers:** NCT01462942, M/40464/30 (AstraZeneca)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A centralised interactive voice-response system
Allocation concealment (selection bias)	Low risk	A centralised interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Major adverse cardiovascular events (MACE; a composite of total cardiovascular death, non-fatal MI and non-fatal stroke) were evaluated and classified by an independent, blinded adjudication committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout low and even among the groups of interest (aclidinium/formoterol (400/12 μg) 8.8 %, aclidinium (400 μg) 13.0 %, formoterol (12 μg) 11.7%)

Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported in detail.

Singh 2015a

Methods	**Design:** randomised, double-blind, placebo- and active-controlled parallel-group study **Duration:** 12 weeks **Location:** Belgium, Canada, Czech Republic, Denmark, Finland, Germany, South Africa, Spain, UK, USA
Participants	**Population** 1. Tiotropium/olodaterol 5/5 μg (203) 2. Tiotropium 5 μg (203) **Baseline characteristics:** age 64.8 (SD 8.4) female:male 331:481 **Inclusion criteria** 1. Diagnosis COPD 2. Relatively stable airway obstruction with post FEV1 $\geq$ 30 and < 80% predicted normal and post FEV1/FVC < 70% 3. Male or female, $\geq$ 40 years of age 4. Smoking history > 10 pack-years **Exclusion criteria** 1. Significant diseases other than COPD 2. History of asthma 3. COPD exacerbation in previous 3 months 4. Completion of pulmonary rehabilitation programme within previous 6 weeks or current participation in pulmonary rehabilitation programme 5. Pregnant or nursing women 6. Inability to comply with pulmonary medication restrictions
Interventions	1. Tiotropium/olodaterol 2. Tiotropium **Inhaler device:** Respimat inhaler **Allowed co-medications:** as-needed salbutamol, ICS
Outcomes	**Primary:** FEV1, SGRQ score
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01964352, 1237.25

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, not defined but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively low in both included groups (tiotropium 5.4%, tiotropium/olodaterol 4.1%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Singh 2015a&b

Methods	**Design:** randomised, double-blind, placebo- and active-controlled parallel-group study **Duration:** 12 weeks **Location:** see Singh 2015a and Singh 2015b
Participants	**Population:** see Singh 2015a and Singh 2015b **Baseline characteristics:** see Singh 2015a and Singh 2015b **Inclusion criteria** 1. Diagnosis COPD 2. Relatively stable airway obstruction with post FEV1 ≥ 30 and < 80% predicted normal and post FEV1/ FVC < 70% 3. Male or female patients, ≥ 40 years of age 4. Smoking history more than 10 pack-years **Exclusion criteria** 1. Significant diseases other than COPD 2. History of asthma 3. COPD exacerbation in previous 3 months 4. Completion of pulmonary rehabilitation programme within previous 6 weeks or current participation in pulmonary rehabilitation programme 5. Pregnant or nursing women 6. Inability to comply with pulmonary medication restrictions
Interventions	1. Tiotropium/olodaterol 2. Tiotropium **Inhaler device:** Respimat inhaler **Allowed co-medications:** as-needed salbutamol, ICS
Outcomes	**Primary:** FEV1, SGRQ score
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01964352, 1237.25, NCT02006732, 1237.26

Singh 2015a&b *(Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised, not defined but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively low in both included groups (See Singh 2015a and Singh 2015b) .
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Singh 2015b

Methods	**Design:** randomised, double-blind, placebo- and active-controlled parallel-group study **Duration:** 12 weeks **Location:** Australia, Austria, Canada, Germany, Greece, New Zealand, Norway, Slovakia, South Africa, Sweden, USA
Participants	**Population** 1. Tiotropium/olodaterol 5/5 μg (202) 2. Tiotropium 5 μg (203) **Baseline characteristics:** age 64.6 (SD 8.4) **Inclusion criteria** 1. Diagnosis COPD 2. Relatively stable airway obstruction with post FEV1 $\geq$ 30 and < 80% predicted normal and post FEV1/FVC < 70% 3. Male or female patients, 40 years of age or more 4. Smoking history more than 10 pack-years **Exclusion criteria:** 1. Significant diseases other than COPD 2. History of asthma 3. COPD exacerbation in previous 3 months 4. Completion of pulmonary rehabilitation programme within previous 6 weeks or current participation in pulmonary rehabilitation programme 5. Pregnant or nursing women

Singh 2015b (*Continued*)

	6. Inability to comply with pulmonary medication restrictions
Interventions	1. Tiotropium/olodaterol 2. Tiotropium **Inhaler device:** Respimat inhaler **Allowed co-medications:** as-needed salbutamol, ICS
Outcomes	Primary Outcome Measures: FEV1, SGRQ score.
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT02006732, 1237.26

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, not defined but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively low in both included groups (tiotropium 2.0%, tiotropium/olodaterol 5.9%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Singh 2015c

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial **Duration:** 12 weeks **Location:** 8 countries (mainly EU), 79 centres
Participants	**Population** 1. Umeclidinium/vilanterol 62.5/25 μg (358) 2. Fluticasone propionate/salmeterol 50/250 μg (358) **Baseline characteristics** Age: 61.6 years (SD 8.0)

	Male/female: 515/201 % predicted FEV1: 50.6% (SD 10.7%) **Inclusion criteria:** % predicted FEV1 30%-70%, mMRC $\geq$ 2, without recent exacerbation **Exclusion criteria:** pregnancy/breast feeding, asthma, other respiratory disorders, clinically significant comorbidities, hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist, corticosteroid, history of COPD exacerbation: a documented history of at least 1 COPD exacerbation in the 12 months prior to visit 1, recent lung resection < 12 months, LTOT > 12 h/d, drug or alcohol abuse
Interventions	1. Umeclidinium/vilanterol (62.5/25 μg). LAMA/LABA 2. Salmeterol/fluticasone (50/500 μg) twice daily. LABA/ICS **Inhaler device:** 1. Umeclidinium/vilanterol: dry white powder DPI 2. Fluticasone propionate/salmeterol: Accuhaler/Diskus **Allowed co-medications:** SABA as rescue
Outcomes	**Primary:** CFB in 0-24 h weighted mean serial FEV1 at day 84
Notes	**Funding:** GlaxoSmithKline **Identifiers:** NCT01822899, DB2116134 (GSK)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK)
Allocation concealment (selection bias)	Low risk	Central randomisation schedule was generated using a validated computer system (RanAll, GSK)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator and treating physician were kept blinded unless an emergency arose
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rate was low and even between active comparators, 6.7% in umeclidinium/vilanterol arm and 5.0% in salmeterol/fluticasone arm
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

Szafranski 2003

Methods	**Design**: randomised, double-blind, placebo-controlled, parallel-group, multicentre study **Duration**: 12 months (+ 2-week run-in period) **Location**: 89 centres from 11 countries
Participants	**Population**: 812 participants were randomised to 1. formoterol 12 μg twice daily (201) 2. budesonide 400 μg twice daily (198) 3. formoterol/budesonide combination 9/320 μg twice daily (208) 4. placebo (205) **Baseline characteristics** Age (mean years): formoterol 63, budesonide 64, formoterol/budesonide 64, placebo 65 % male: formoterol 76, budesonide 80, formoterol/budesonide 76, placebo 83 % FEV1 predicted: formoterol 36, budesonide 37, formoterol/budesonide 36, placebo 36 Pack-years (mean): formoterol 45, budesonide 44, formoterol/budesonide 44, placebo 45 **Inclusion criteria**: men and women aged $\geq$ 40 years; symptoms for > 2 years; history of at least 10 pack-years **Exclusion criteria**: history of asthma or seasonal rhinitis before 40 years of age; relevant CVDs; use of beta-blockers; current respiratory tract disorders other than COPD or any other significant diseases or disorders; requiring regular use of oxygen therapy; exacerbation during run-in
Interventions	1. Formoterol 12 μg twice daily (LABA) 2. Budesonide 400 μg twice daily (ICS) 3. Formoterol/budesonide 9/320 μg twice daily (LABA/ICS) 4. Placebo **Inhaler device**: dry powder Turbuhaler **Allowed co-medications**: terbutaline (0.5 mg) as reliever. Disallowed medication included parenteral steroids, oral steroids, antibiotics and nebulised treatment from 4 weeks before; ICS from 2 weeks before; inhaled LABA from 48 h before; inhaled SABA from 6 h before; other bronchodilators from 6-48 h before
Outcomes	SGRQ, COPD exacerbations, FEV1, vital capacity, morning and evening PEF, diary card data
Notes	**Funding**: AstraZeneca **Identifier(s)**: SD-039-CR-0629 (AstraZeneca)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A total of 812 participants were randomised (no other details, industry-sponsored)
Allocation concealment (selection bias)	Unclear risk	No details

Szafranski 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (presumed participant and investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded (presumed investigators were also outcomes assessors)
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal high and uneven between groups (formoterol 32%, formoterol/budesonide 28%). Higher withdrawal rate due to COPD deterioration with formoterol (14%) vs formoterol/budesonide (10%). An ITT analysis was used
Selective reporting (reporting bias)	High risk	QoL (primary) stated as outcome but not reported in enough detail to include in meta-analysis. Safety and exacerbation outcomes were not reported in enough detail

Tashkin 2008

Methods	**Design**: randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multicentre study **Duration**: 6 months (+ 2-week run-in period) **Location**: 194 centres in the USA, Czech Republic, the Netherlands, Poland and South Africa
Participants	**Population**: 1704 participants were randomised to 1. formoterol (284), 2. budesonide (275), 3. formoterol/budesonide combination: three doses (281, 277 and 287, one of which was not included in the review as they were delivered in separate inhalers) 4. and placebo (300) **Baseline characteristics** Age (mean years): formoterol 63.5, budesonide 63.4, formoterol/budesonide (9/160) 63.6, formoterol/budesonide (9/320) 63.1, placebo 63.2 % male: formoterol 65.5, budesonide 67.6, formoterol/budesonide (9/160) 64.4, formoterol/budesonide (9/320) 67.9, placebo 69 % FEV1 predicted: formoterol 39.6, budesonide 39.7, formoterol/budesonide (9/160) 39.9, formoterol/budesonide (9/320) 39.1, placebo 41.3 Pack-years (median): formoterol 40, budesonide 41, formoterol/budesonide (9/160) 40, formoterol/budesonide (9/320) 40, placebo 40 **Inclusion criteria**: male and female current or former smokers; history of at least 10 pack-years; clinical diagnosis of COPD; > 40 years; symptoms for > 2 years; at least 1 exacerbation treated with systemic corticosteroids and/or antibacterials within 1-12 months before screening **Exclusion criteria**: history of asthma or seasonal rhinitis before age 40; significant/

	unstable CVD; significant respiratory tract disorder other than COPD; homozygous alpha1-antitrypsin deficiency or other clinically significant co morbidities precluding participation
Interventions	1. Formoterol 12 μg twice daily (LABA) 2. Budesonide 320 μg twice daily (ICS) 3. Formoterol/budesonide 9/160 μg twice daily in one inhaler (LABA/ICS) 4. Formoterol/budesonide 9/320 μg twice daily in one inhaler (LABA/ICS) 5. Placebo **Inhaler device**: DPI **Allowed co-medications**: allowed medications were ephedrine-free antitussives and mucolytics; nasal corticosteroids; stable-dose non-nebulised ipratropium; cardioselective beta-adrenoceptor antagonists; salbutamol as rescue; oral steroids, xanthines, inhaled beta-agonists and ipratropium as medication for exacerbations. Medications disallowed during the study period were long-acting anticholinergics; inhaled LABAs or SABAs (other than salbutamol); oral beta-adrenoreceptor agonists; ephedrine; leukotriene receptor agonists and xanthine derivatives except for short-term use
Outcomes	SGRQ including number of people reaching threshold for minimal clinically important difference from baseline (4 units), COPD exacerbations per patient year, pre-dose FEV1 and 1-hour post-dose FEV1, dyspnoea, morning and evening PEF
Notes	**Funding**: AstraZeneca **Identifier(s)**: NCT00206154, D5899C00002 (SHINE)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants were randomised in balanced blocks according to a computer-generated randomisation scheme at each site
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To maintain blinding, participants received both a pressurised MDI and a DPI containing either active treatment or placebo, or combinations of active treatment and placebo, as appropriate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy. Investigators were blinded (presumed investigators were also outcomes assessors)
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal rates were higher with formoterol (21.5% formoterol, 14.1% budesonide/formoterol 320/9, and

		13.5% budesonide/formoterol 160/9) and more participants were discontinue due to AE with formoterol (12% formoterol, 7.6% budesonide/formoterol 320/9 μg, and 7.1% budesonide/formoterol 160/9 μg)). The efficacy analysis set included all randomised patients who received at least one dose of study medication and contributed sufficient data for at least one co-primary or secondary efficacy endpoint
Selective reporting (reporting bias)	Low risk	All stated outcomes were reported in full and included in the quantitative synthesis

Tashkin 2009

Methods	**Design:** randomised, double-blind, active-control, parallel-group trial **Duration:** 12 weeks **Location:** 35 centres across the USA, of which the majority were primary care centres
Participants	**Population:** 255 adults with a clinical history of COPD randomised to 1. tiotropium + formoterol (124 participants) 2. tiotropium (131 participants) **Baseline characteristics:** mean age 64 years. COPD severity mild-severe. 67% men **Inclusion criteria:** men and non-pregnant women aged > 40 years who had a clinical history of COPD. Each participant had a post-bronchodilator FEV1 < 70% and > 30% predicted normal or > 0.75 L, whichever was less, at run-in, and FEV1/FVC < 0.70 at screening and run-in. Daytime and/or night-time symptoms of COPD, including dyspnoea, must have been present on ≥ 4 of the 7 days before the baseline visit **Exclusion criteria:** current or previous history of asthma or other significant medical condition that may have interfered with study treatment as assessed by the investigator, smoking cessation within the previous 3 months, ventilator support for respiratory failure within the previous year, the use of oxygen (≥ 2 L/min or for > 2 h/d), initiation of pulmonary rehabilitation within the previous 3 months, the requirement for nasal continuous positive airway pressure or bilevel positive airway pressure, clinically significant lung disease other than COPD (i.e. bronchiectasis, sarcoidosis, pulmonary fibrosis, TB), sleep apnoea, chronic narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder neck obstruction, and the need for chronic or prophylactic antibiotic therapy
Interventions	**Inhaler device** 1. Formoterol (Foradil Aerolizer) 12 μg twice daily and tiotropium (HandiHaler) 18 μg once daily in the morning delivered via 2 separate inhalers 2. Formoterol-matched placebo twice daily and tiotropium 18 μg once daily delivered via 2 separate inhalers **Allowed co-medications:** as-needed albuterol, ICS
Outcomes	**Primary:** normalised AUC for FEV1 measured 0-4 h post-morning dose at the last visit **Secondary:** changes from baseline in trough (mean of values obtained 10 and 30 min pre-dose) FEV1 and FVC, weekly morning and evening PEF, symptom severity scores,

Tashkin 2009 *(Continued)*

	TDI, and health-related QoL (SGRQ) scores, number and severity of exacerbations, the global therapeutic response, discontinuations because of worsening COPD, and % participants achieving targeted improvements in the SGRQ and TDI scores, use of rescue albuterol, nocturnal awakenings requiring rescue albuterol, changes in study or concomitant medications, and AEs
Notes	**Funding:** Schering Corporation **Identifiers:** NCT00139932

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised sequentially as they qualified for the study according to a pre-generated computer code labelled on the medication kit
Allocation concealment (selection bias)	Low risk	Participants were randomised sequentially as they qualified for the study according to a pre-generated computer code labelled on the medication kit
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of withdrawals in the different groups was relatively low but uneven (14.5% with formoterol + tiotropium, 6.1% with tiotropium + placebo)
Selective reporting (reporting bias)	Low risk	Results for all listed primary and secondary outcomes were reported

Tashkin 2012a

Methods	See Tashkin 2012a&b
Participants	See Tashkin 2012a&b
Interventions	See Tashkin 2012a&b
Outcomes	See Tashkin 2012a&b

Tashkin 2012a (*Continued*)

Notes	**Funding:** Merck & Co/Schering-Plough **Identifiers:** NCT00383435, Merck P04230AM4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sponsor's statistician produced a computer-generated randomisation schedule with treatment codes in blocks using computer software. Randomisation was stratified according to the participant's smoking status at the time of randomisation
Allocation concealment (selection bias)	Low risk	Randomised treatment assignment was provided to the investigative site by means of an interactive voice-response system at the time participants were randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Protocol describes the study masking as double-blind (participant, investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A prospective statistical analysis plan for evaluation of pooled results was completed before unblinding of the 2 studies
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Tashkin 2012a&b
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports and clinicaltrials.gov

Tashkin 2012a&b

Methods	**Design**: randomised, double-blind, placebo-controlled trial **Duration**: 6 months (+ 2-week run-in period) **Location**: 131 centres located in South America, Asia, Africa, Europe andNorth America
Participants	**Population**: 1055 participants were randomised to 1. formoterol (209) 2. mometasone (210) 3. formoterol/mometasone combination (two doses; 217 and 207) 4. placebo (212) **Baseline characteristics** Age (mean years): formoterol 59.6, mometasone 59.8, formoterol/mometasone (10/400 μg) 59.7, formoterol/mometasone (10/200 μg) 60.9, placebo 58.8 % male: formoterol 72.7, mometasone 78.1, formoterol/mometasone (10/400 μg) 78.8, formoterol/mometasone (10/200 μg) 77.8, placebo 80.2 % FEV1 predicted: not reported Pack-years (mean): formoterol 40.3, mometasone 40.0, formoterol/mometasone (10/

	400 μg) 39.7, formoterol/mometasone (10/200 μg) 41.7, placebo 40.3 **Inclusion criteria**: men and women aged ≥ 40 years; history of at least 10 pack-years; moderate-severe COPD for at least 2 years; predicted FEV1 between 25% and 60% normal **Exclusion criteria**: exacerbation in the 4 weeks before randomisation; significant medical illness; diagnosis of asthma, lung cancer or alpha1-antitrypsin deficiency, lobectomy, pneumonectomy, lung volume reduction surgery or ocular problems
Interventions	1. Formoterol 10 μg twice daily (LABA) 2. Mometasone 400 μg twice daily (ICS) 3. Formoterol/mometasone 10/400 μg twice daily (LABA/ICS) 4. Formoterol/mometasone 10/200 μg twice daily (LABA/ICS) 5. Placebo (placebo) **Inhaler device**: metered dose **Allowed co-medications**: participants were given open-label, SABA/short-acting anticholinergic fixed-dose combination to use as relief medication throughout the study All long-acting COPD treatments (LABA, ICS, LABA/ICS FDC or long-acting anticholinergics), supplemental oxygen and beta-blocking agents were not allowed during the study period
Outcomes	SQRQ, reported as both final scores and the number of people experiencing a MCID (improvement or worsening by 4 units), COPD exacerbations, serial FEV1 post-dose, standardised FEV1 AUC, systemic and ocular effects
Notes	**Funding**: Merck & Co/Schering-Plough **Identifier(s)**: NCT00383435 (Tashkin 2012a), NCT00383721 (Tashkin 2012b), P04229AM4, P04230AM4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The sponsor's statistician produced a computer-generated randomisation schedule with treatment codes in blocks using computer software. Randomisation was stratified according to the participant's smoking status at the time of randomisation
Allocation concealment (selection bias)	Low risk	Randomised treatment assignment was provided to the investigative site by means of an interactive voice-response system at the time participants were randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Protocol describes the study masking as double-blind (participant, investigator)

Tashkin 2012a&b (*Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	A prospective statistical analysis plan for evaluation of pooled results was completed before unblinding of the 2 studies (Tashkin 2012a and Tashkin 2012b).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rates were relatively low and even among active comparators (18.9% in formoterol/mometasone 10/400 μg, 18.4% in formoterol/mometasone 10/200 μg, and 17.7% in formoterol)
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports and clinicaltrials.gov

Tashkin 2012b

Methods	See Tashkin 2012a&b
Participants	See Tashkin 2012a&b
Interventions	See Tashkin 2012a&b
Outcomes	See Tashkin 2012a&b
Notes	**Funding:** Merck & Co/Schering-Plough **Identifiers:** NCT00383721, Merck P04229AM4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sponsor's statistician produced a computer-generated randomisation schedule with treatment codes in blocks using computer software. Randomisation was stratified according to the participant's smoking status at the time of randomisation
Allocation concealment (selection bias)	Low risk	Randomised treatment assignment was provided to the investigative site by means of an interactive voice-response system at the time participants were randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Protocol describes the study masking as double-blind (participant, investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A prospective statistical analysis plan for evaluation of pooled results was completed before unblinding of the 2 studies

Incomplete outcome data (attrition bias) All outcomes	Low risk	See Tashkin 2012a&b
Selective reporting (reporting bias)	Low risk	Study was prospectively registered, and all results were available from the published reports and clinicaltrials.gov

To 2012

Methods	**Design:** multicentre, randomised, double-blind, placebo-controlled, parallel-group study **Duration:** 12 weeks **Location:** Hong Kong, India, Japan, Korea, Republic of, Singapore, Taiwan
Participants	**Population** 1. Indacaterol 150 μg (114) 2. Indacaterol 300 μg (116) **Baseline characteristics:** age 66.7 (SD 8.38) female:male 12:335 **Inclusion criteria** Diagnosis of moderate-to-severe COPD, as classified by the GOLD criteria and: 1. Smoking history of at least 20 pack-years 2. Post-bronchodilator FEV1 < 80% and $\geq$ 30% of the predicted normal value 3. Post-bronchodilator FEV1/FVC < 70% **Exclusion criteria:** 1. Hospitalized for a COPD exacerbation in the 6 weeks prior to screening or during the 14-day run-in period prior to randomisation 2. LTOT (> 15 h/d) for chronic hypoxaemia 3. Respiratory tract infection within 6 weeks prior to screening 4. Concomitant pulmonary disease 5. History of asthma 6. Diabetes type 1 or uncontrolled diabetes type 2 7. Lung cancer or a history of lung cancer 8. Active cancer or a history of cancer with < 5 years disease-free survival time 9. History of long QT syndrome or whose QTc interval (Bazett's) measured at screening or randomisation is prolonged 10. Vaccinated with live attenuated vaccines within 30 days prior to screening or during the run-in period 11. Inability to successfully use a DPI device or perform spirometry measurements
Interventions	**Inhaler device** 1. Indacaterol: powder-filled capsules with a single-dose DPI **Allowed co-medications:** as-needed salbutamol, ICS
Outcomes	**Primary:** trough FEV1 24 h post-dose at the end of treatment (week 12 + 1 day, day 85)
Notes	**Funding:** Novartis **Identifiers:** NCT00794157, CQAB149B1302

Risk of bias

To 2012 (*Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised (1:1:1) using a validated automated system
Allocation concealment (selection bias)	Low risk	Participants were randomised (1:1:1) using a validated automated system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively low and even in both included groups (8.8% in indacaterol 150 μg and 8.6% in indacaterol 300 μg group)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Troosters 2016

Methods	**Design:** randomised, partially double-blinded, placebo-controlled parallel-group study **Duration:** 12 weeks **Location:** Australia, Austria, Belgium, Canada, Denmark, Germany, New Zealand, Poland, Portugal, UK, USA
Participants	**Population** 1. Tiotropium/olodaterol 5/5 μg (76) 2. Tiotropium 5 μg (76) **Baseline characteristics:** age 64.8 (SD 6.6) female:male 103:200 **Inclusion criteria** 1. Signed informed consent consistent with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice guidelines prior to participation in the trial, which includes medication washout and restrictions 2. Diagnosis of COPD and must meet the following spirometric criteria: i) relatively stable airway obstruction with a post-bronchodilator FEV1 $\geq$30% and < 80% of predicted normal ii) GOLD grade 2-3, iii) post-bronchodilator Tiffeneau index < 70% at visit 1 3. Male or female patients, aged $\geq$ 40 years and $\leq$ 75 years 4. Current or ex-smokers with a smoking history of more than 10 pack-years. Patients who had never smoked cigarettes were excluded. **Exclusion criteria**

	1. Significant disease other than COPD 2. Clinically relevant abnormal baseline haematology, blood chemistry, or urinalysis 3. History of asthma 4. Diagnosis of paroxysmal tachycardia (> 100 bpm) 5. History of MI within 1 year of screening visit 6. Unstable or life-threatening cardiac arrhythmia 7. Hospitalised for heart failure within the past year 8. Known active TB 9. Malignancy treated by resection, radiation therapy or chemotherapy within last 5 years 10. History of life-threatening pulmonary obstruction and current chronic respiratory failure 11. History of cystic fibrosis 12. Clinically evident bronchiectasis 13. Undergone thoracotomy with pulmonary resection 14. Currently being treated with any oral ß-adrenergics 15. Currently being treated with OCS medication at unstable doses (i.e. < 6 weeks on a stable dose) or at doses > the equivalent of 10 mg of prednisone/d or 20 mg every other day. 16. Regular use of daytime oxygen therapy for > 1 h/d and in the investigators' opinion will be unable to abstain from the use of oxygen therapy during clinic visits
Interventions	1. Tiotropium + olodaterol 2. Tiotropium **Inhaler device:** Respimat Inhaler **Allowed co-medications:** salbutamol as rescue, ICS
Outcomes	**Primary:** endurance time during endurance shuttle walk test to symptom limitation After 8 Weeks
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT02085161

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Partially double-blinded, as it was not possible to blind the group receiving exercise training
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of outcome assessors

Troosters 2016 (*Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was relatively low but uneven between included arms (tiotropium 13.2%, tiotropium/olodaterol 6.6%)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Vincken 2014

Methods	**Design:** multicentre, randomised, double-blind, parallel-group study **Duration:** 12 weeks **Location:** Belgium, Bulgaria, Greece, Hungary, Ireland, Russian Federation, Slovakia, Spain, Turkey, UK
Participants	**Population** 1. Indacaterol + glycopyrronium 110/50 μg (226) 2. Indacaterol 150 μg (221) **Baseline characteristics:** age 63.7 (SD 8.07) female:male 81/366 **Inclusion criteria** 1. Moderate-severe stable COPD stage 2 or stage 3 according to GOLD criteria 2. Post-bronchodilator FEV1 $\geq$ 30% and/or < 80% of the predicted normal, and a post-bronchodilator FEV1/FVC < 0.70 at screening 3. Current or ex-smokers who have a smoking history of at least 10 pack-years 4. Symptomatic patients according to daily diary data **Exclusion criteria** 1. Pregnant or nursing (lactating) women 2. Women of child-bearing potential unless using adequate contraception 3. Type I or uncontrolled type 2 diabetes 4. History of long time interval between start of Q wave and end of T wave in the heart's electrical cycle (QT) syndrome or whose QTc measured at screening (visit 2) (Fridericia's method) is prolonged 5. Paroxysmal (e.g. intermittent) atrial fibrillation 6. Clinically significant ECG or laboratory abnormality at screening (visit 2)
Interventions	**Inhaler device:** glycopyrronium (NVA237) 50 µg and indacaterol 150 µg supplied as blistered capsules for inhalation **Allowed co-medications:** as-needed salbutamol, ICSs
Outcomes	**Primary:** trough FEV1 (time frame: 12 weeks)
Notes	**Funding:** Novartis **Identifiers:** NCT01604278, CNVA237A2316

Risk of bias

Bias	Authors' judgement	Support for judgement

Vincken 2014 (*Continued*)

Random sequence generation (selection bias)	Low risk	An automated, interactive, voice-response technology
Allocation concealment (selection bias)	Low risk	An automated, interactive, voice-response technology
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, site staff, assessors and data analysts were blind to the identity of the treatment from the time of randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively low and even in both included groups (6.2% in indacaterol + glycopyrronium and 5.8% in indacaterol group)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Vogelmeier 2008

Methods	**Design**: randomised, partially blinded, placebo-controlled trial **Duration**: 6 months (+ 2-week run-in) **Location**: outpatient and specialist clinics at 86 centres in 8 countries
Participants	**Population**: 847 participants were randomised to 1. tiotropium + formoterol (207) 2. formoterol (210) 3. tiotropium (221) 4. placebo (209) - not included in this review **Baseline characteristics** Age (mean years): formoterol 61.8, tiotropium 63.4, placebo 62.5 % male: formoterol 75.7, tiotropium 79.2, placebo 77.5 % FEV1 predicted: formoterol 51.6, tiotropium 51.6, placebo 51.1 Pack-years (mean): formoterol 35.4, tiotropium 38.6, placebo 40.1 **Inclusion criteria**: men and women aged $\geq$ 40; history of at least 10 pack-years; FEV1 < 70% predicted normal; FEV1/FVC < 70% **Exclusion criteria**: respiratory tract infection or hospitalised for an acute exacerbation within the month before screening; clinically significant condition other than COPD such as ischaemic heart disease
Interventions	1. Tiotropium 18 μg once daily (LAMA) + formoterol 10 μg twice daily (LABA) 2. Formoterol 10 μg twice daily (LABA) 3. Tiotropium 18 μg once daily (LAMA) - open-label

	4. Placebo **Inhaler device**: 1. Multi-dose DPI 2. Tiotropium open-label **Allowed co-medications:** salbutamol as rescue (but not in the 8 h before a study visit); ICS were allowed at a stable daily dose. Any participants receiving fixed combinations of ICS and beta2-agonists were switched to receive the same dose of ICS and on-demand salbutamol
Outcomes	SGRQ, COPD exacerbations, FEV1 and FEV measured at 5 min, 2 h and 3 h post-dose, PEF, 6MWD, haematology, blood chemistry, ECG, diary card data
Notes	**Funding**: Novartis **Identifier(s)**: NCT00134979, CFOR258F2402

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was not stratified (no other information given but assumed to follow convention Novartis sequence generation methods)
Allocation concealment (selection bias)	Low risk	Randomisation was not stratified (no other information given but assumed to follow convention Novartis sequence generation methods)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Tiotropium was delivered open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Tiotropium was delivered open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rate was relatively low (12%-13%) and even across active comparators. The ITT population consisted of all randomised participants who received $\geq$ 1 dose of study medication. This population was used for efficacy and safety analyses
Selective reporting (reporting bias)	High risk	FEV1 and SGRQ outcomes only provided in graphical form only with inexact P value

Vogelmeier 2011

Methods	**Design**: randomised, double-blind, double-dummy, parallel-group study **Duration**: 1 year (+ 2-week run-in) **Location**: 725 centres in 25 countries
Participants	**Population**: 7376 participants were randomised to 1. tiotropium (3707) 2. salmeterol (3669) **Baseline characteristics** Age (mean years): salmeterol 62.8, tiotropium 62.9 % male: salmeterol 74.9, tiotropium 74.4 % FEV1 predicted: salmeterol 49.4, tiotropium 49.2 Pack-years (mean): salmeterol 37.8, tiotropium 38.8 **Inclusion criteria**: ≥ 40 years of age; smoking history of ≥ 10 pack-years; a diagnosis of COPD; a FEV1 after bronchodilation of < 70% of the predicted value; a ratio of FEV1/FVC of < 70%, and a documented history of at least one exacerbation leading to treatment with systemic glucocorticoids or antibiotics or hospitalisation within the previous year **Exclusion criteria**: significant disease other than COPD; diagnosis of asthma; life-threatening pulmonary obstruction, or a history of cystic fibrosis; active TB; narrow-angle glaucoma; MI or hospital admission for heart failure within the year prior to visit 1; cardiac arrhythmia requiring medical or surgical treatment; severe CVD; hypersensitivity to components of study drugs; respiratory infection or exacerbation in the 4 weeks prior to visit 1
Interventions	1. Salmeterol 50 μg twice daily (LABA) + HandiHaler placebo 2. Tiotropium 18 μg once daily (LAMA) + pMDI placebo **Inhaler device**: HandiHaler and pMDI **Allowed co-medications**: participants' usual COPD medications except for anticholinergic drugs and LABA, during the double blind treatment phase
Outcomes	**Primary:** time to first exacerbation **Secondary:** time-to-event end points, number-of-event end points, SAEs, and death
Notes	**Funding**: Boehringer Ingelheim and Pfizer **Identifier(s)**: NCT00563381

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list was generated by the sponsor using a validated system involving a pseudo random-number generator. Participants were randomised in a 1:1 ratio in blocks of 4, with equal allocation of treatment within each block per country site
Allocation concealment (selection bias)	Low risk	Participants were randomised to treatment via an interactive voice-response system

Vogelmeier 2011 (*Continued*)

		(Perceptive Informatics Inc., Berlin, Germany)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding was maintained by allocation of a dummy placebo MDI to those randomised to the tiotropium arm and a dummy placebo HandiHaler to those in the salmeterol arm. Tiotropium and placebo capsules were identical in size and colour and were therefore indistinguishable
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A committee assessing cause of death was blind to treatment group. Review authors judged that other outcomes were blind too
Incomplete outcome data (attrition bias) All outcomes	Low risk	The efficacy and safety analyses included all the participants who underwent randomisation and who received ≥ 1 dose of the study medication. Fewer participants in the tiotropium group than in the salmeterol group withdrew from the study prematurely: 585 participants (15.8%) vs 648 participants (17.7%) but both were judged to be low over a year and considering imputation of missing values
Selective reporting (reporting bias)	Low risk	Outcomes were well reported in the publications and on clinicaltrials.gov

Vogelmeier 2013a

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled study **Duration:** 26 weeks **Location:** 10 countries and 92 centres (mainly EU countries)
Participants	**Population** 1. Indacaterol/glycopyrronium (258) 2. Fluticasone propionate/salmeterol (264) **Baseline characteristics:** Age: indacaterol/glycopyrronium, 63.2 years (SD 8.2); salmeterol/fluticasone , 63.4 years (SD 7.7) Male/female: indacaterol/glycopyrronium, 181/77; salmeterol/fluticasone , 189/75 % predicted FEV1: indacaterol/glycopyrronium, 60.5% (SD 10.5%); salmeterol/fluticasone , 60.0% (SD 10.7%) **Inclusion criteria:** COPD stage 2/3 without recent exacerbation **Exclusion criteria:** pregnancy, significant comorbidities, history of malignancy, COPD exacerbations within the last year, LTOT, asthma, other concomitant lung disease, lung

	transplant
Interventions	1. Indacaterol/glycopyrronium (110/50 μg) once daily 2. Salmeterol/fluticasone (50/500 μg) twice daily **Inhaler device:** 1. indacaterol/glycopyrronium: DPI 2. fluticasone propionate/salmeterol: dry inhalation powder delivered via Accuhaler **Allowed co-medications:** SABA as rescue
Outcomes	Primary outcome: FEV1 AUC (0-12 h)
Notes	**Funding:** Novartis **Identifiers:** NCT01315249, CQVA149A2313

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Investigators used an automated, interactive-response technology to assign randomisation numbers to participants
Allocation concealment (selection bias)	Low risk	Investigators used an automated, interactive-response technology to assign randomisation numbers to participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation data were kept strictly confidential until the time of unblinding and were not accessible by anyone else involved in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal was relatively low and even between active comparators, 17.0% in indacaterol/glycopyrronium arm and 17.0% in salmeterol/fluticasone arm
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

Vogelmeier 2016

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial **Duration:** 24 weeks **Location:** 14 countries and 126 centres (mainly EU countries)
Participants	**Population** 1. Aclidinium/formoterol (467) 2. Fluticasone propionate/salmeterol (466) **Baseline characteristics:** age: 63.4 years (SD 7.8). Male/female: 607/326 **Inclusion criteria:** % predicted FEV1 < 80%, CAT ≥ 10, without recent exacerbation **Exclusion criteria:** pregnancy, significant comorbidities, history of malignancy, COPD exacerbations within the last 3 months, LTOT (> 15 h/d), asthma, other concomitant lung disease
Interventions	1. Aclidinium/formoterol (400/12 μg) twice daily 2. Salmeterol/fluticasone (50/500 μg) twice daily **Inhaler device:** 1. Aclidinium/formoterol: Genuair/Pressair 2. Fluticasone propionate/salmeterol: Accuhaler **Allowed co-medications:** salbutamol as rescue
Outcomes	**Primary:** peak FEV1 at week 24
Notes	**Funding:** Almirall/ AstraZeneca **Identifiers:** NCT01908140, M/40464/39, 2013-000116-14

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry- funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal was relatively low and even between active comparators, 14.1% in aclidinium/formoterol arm and 17.0% in salmeterol/fluticasone arm

Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

Vogelmeier 2017

Methods	**Design:** prospective, multicentre, randomised open-label study **Duration:** 12-weeks **Location:** 673 centres in 23 countries: Austria (12), Belgium (40), Czech Republic (35), Denmark (5), Estonia (6), France (32), Germany (236), Greece (5), Hungary (18), Ireland (6), Italy (72), Latvia (7), Lithuania (9), Norway (12), Poland (9), Portugal (11), Romania (8), Russia (18), Slovakia (16), Slovenia (4), Spain (50), Sweden (12), UK (50)
Participants	**Population:** • LABA/ICS 274 • Indacaterol/glycopyrronium (822) **Baseline characteristics:** age LABA/ICS 64.4 (SD 9), indacaterol/glycopyrronium 64.7 (SD 8.7); female/male: LABA/ICS 106/168, indacaterol/glycopyrronium 286/536 **Inclusion criteria** 1. Male and female adults aged $\geq$ 40 years 2. Moderate COPD according to the GOLD 2013 criteria 3. Current or ex-smokers who have a smoking history of at least 10 pack-years 4. Airflow limitation indicated by a postbronchodilator FEV1 $\geq$ 50% and < 80% of the predicted normal value and a post-bronchodilator FEV1/FVC < 0.7 at visit 2 5. mMRC score $\geq$ 1 at visit 1 **Exclusion criteria** 1. Narrow-angle glaucoma 2. Urinary retention 3. Severe renal impairment, including those with end-stage renal disease requiring dialysis 4. Asthma 5. Malignancy of any organ system 6. Documented history of > 1 COPD exacerbation requiring treatment with systemic corticosteroids or antibiotics and/or hospitalisation in the previous 12 months 7. Clinically significant condition such as (but not limited to): unstable ischaemic heart disease, left ventricular failure (NYHA Class 3 & 4), history of MI, arrhythmia (excluding chronic stable atrial fibrillation) 8. BMI > 40 kg/m^2
Interventions	**Inhaler device** 1. Glycopyrronium 50 µg capsule for inhalation via DPI 2. Indacaterol maleate and glycopyrronium bromide FDC (110/50 µg) capsule for inhalation via DPI 3. SABA 4. LABA 5. Short-acting muscarinic antagonist 6. ICS **Allowed co-medications:** not described. The list of prohibited medication (Table 5-2)

	not available
Outcomes	**Primary:** trough FEV1 at week 12 for group: glycopyrronium vs short-acting bronchodilators (SABA and/or Short-acting muscarinic antagonist as monotherapy or in free or FDC)
Notes	**Funding:** Novartis **Identifiers:** NCT01985334, CQVA149A3401

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was relatively low and even between groups (14.6% in LABA/ICS group and 19% in indacaterol/glycopyrronium group)
Selective reporting (reporting bias)	Low risk	Outcomes stated on pre-registered protocol were well reported

Wedzicha 2008

Methods	**Design**: multicentre, randomised, double-blind, double-dummy controlled trial **Duration**: 2 years (+ 2-week run-in) **Location**: 179 centres from 20 countries
Participants	**Population**: 1323 participants were randomised to 1. Tiotropium (665) 2. Salmeterol/fluticasone combination (658) **Baseline characteristics** Age (mean years): tiotropium 65, salmeterol/fluticasone 64 % male: tiotropium 84, Salmeterol/fluticasone 81 % FEV1 predicted: tiotropium 39.4, salmeterol/fluticasone 39.1 Pack-years (mean): tiotropium 39.5, salmeterol/fluticasone 41.3 **Inclusion criteria**: aged 40-80 years, with a smoking history of ≥ 10 pack-years, a

	clinical history of COPD exacerbations, a post-bronchodilator FEV1 of < 50% predicted, reversibility to 400 µg salbutamol $\leq$ 10% predicted FEV1, and a score of $\geq$ 2 on the mMRC dyspnoea scale **Exclusion criteria**: any respiratory disorder other than COPD or who required daily LTOT (> 12 h/d)
Interventions	1. Tiotropium 18 µg once daily (LAMA) + Diskus/Accuhaler placebo 2. Salmeterol/fluticasone 50/500 µg (LABA/ICS) + HandiHaler placebo **Inhaler device**: Diskus/Accuhaler and HandiHaler **Allowed co-medications**: after randomisation, in addition to study medication, participants were allowed SABAs for relief therapy and standardised short courses of oral systemic corticosteroids and/or antibiotics where indicated for treatment of COPD exacerbations
Outcomes	**Primary:** health care utilisation exacerbation rate. **Secondary:** health status measured by SGRQ, mortality, AEs, and study withdrawal
Notes	**Funding**: GlaxoSmithKline **Identifier(s)**: NCT00361959

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a predefined, computer-generated, central randomisation list. Treatment allocation was stratified by centre and smoking status on a 1:1 basis, in line with current guidelines. The block size used was 4
Allocation concealment (selection bias)	Low risk	Telephone-based, interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator and treating physician were kept blinded unless an emergency arose
Incomplete outcome data (attrition bias) All outcomes	High risk	1323 were randomised and comprised the ITT population. Withdrawal was high in both groups and uneven after 2 years (35.3 and 42%). A higher proportion of participants was withdrawn due to COPD exacerbation and consent withdrawal with tiotropium group compared to SFC group

Wedzicha 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	Outcomes were well reported in the publications, and matched the study protocol (although results have not been posted on clinicaltrials.gov)

Wedzicha 2013

Methods	**Design**: randomised, double-blind, parallel-group study **Duration**: 64 weeks **Location**: 345 study locations
Participants	**Population**: 2224 participants were randomised to 1. open-label tiotropium (742) 2. glycopyrronium (741) 3. indacaterol/glycopyrronium (741) **Baseline characteristics** Age (mean years): glycopyrronium 63.1, tiotropium 63.6 % male: glycopyrronium 73.2, tiotropium 75.0 % FEV1 predicted: not reported Pack-years (mean): not reported **Inclusion criteria**: male or female adults aged $\geq$ 40 years, who had signed an informed consent form prior to initiation of any study-related procedure; severe-very severe COPD (stage 3 or 4) according to the GOLD 2008 criteria; current or ex-smokers with a smoking history of at least 10 pack-years (defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years); postbronchodilator FEV1 < 50% of the predicted normal value, and post-bronchodilator FEV1/FVC < 0.70 at visit 2; documented history of at least 1 COPD exacerbation in the previous 12 months that required treatment with systemic glucocorticosteroids and/or antibiotics **Exclusion criteria**: pregnant women or nursing mothers; women of child-bearing potential; requiring LTOT; COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalisation in the 6 weeks prior to visit 1; respiratory tract infection within 4 weeks prior to visit 1; concomitant pulmonary disease; lung lobectomy, or lung volume reduction or lung transplantation; clinically relevant laboratory abnormality or a clinically significant condition; history of asthma, allergic rhinitis, eczema or alpha1 antitrypsin deficiency; contraindication for study drugs
Interventions	1. Indacaterol 110 μg/glycopyrronium 50 μg (QVA149) once daily (LABA/LAMA) 2. Glycopyrronium 50 μg once daily (LAMA) 3. Tiotropium 18 μg once daily (LAMA) - open-label **Inhaler device** 1. Indacaterol 110 μg/glycopyrronium 50 μg capsules for inhalation, once daily delivered via Novartis Single Dose DPI 2. Glycopyrronium was delivered via a Novartis single-dose DPI, and tiotropium was delivered open-label via the HandiHaler **Allowed co-medications**: salbutamol could be taken as needed throughout the study
Outcomes	**Primary:** rate of moderate/severe COPD exacerbations **Secondary:** pre-dose FEV1 and FVC, rescue medication use, and the SGRQ

Wedzicha 2013 (*Continued*)

Notes	**Funding**: Novartis **Identifier(s)**: NCT01120691

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, not defined but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding procedures were sound, but tiotropium was delivered open-label, which introduced bias for these comparisons. Double-blind (participant, caregiver, investigator, outcomes assessor)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding procedures were sound, but tiotropium was delivered open-label, which introduced bias for these comparisons. Double-blind (participant, caregiver, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The full analysis set included > 99% of the randomised population. 25% dropped out overall, and dropout was relatively even across groups (24% and 27%)
Selective reporting (reporting bias)	Low risk	Outcomes were fully reported on clinicaltrials.gov

Wedzicha 2014

Methods	**Design:** a phase 3, double-blind, randomised, 2-arm parallel-group study **Duration:** 48 weeks **Location:** UK
Participants	**Population** 1. Beclomethasone dipropionate/formoterol 200/12 μg (601) 2. Formoterol 12 μg (596) **Baseline characteristics:** age 64.3 female:male 372:818 **Inclusion criteria** 1. Severe COPD 2. At least one COPd exacerbation in previous year **Exclusion criteria** 1. Asthma, allergic rhinitis or other atopic disease 2. Unstable concurrent disease:

	3. Evidence of heart failure
Interventions	**Inhaler device** 1. Beclomethasone dipropionate 100 µg + formoterol fumarate 6 µg/per metered dose 2. Formoterol fumarate 12 µg per metered dose **Allowed co-medications:** as-needed salbutamol, theophylline and tiotropium
Outcomes	**Primary:** exacerbation rate change in pre-dose FEV1 (time frame: 0-4-12-24-36-48 weeks)
Notes	**Funding:** Chiesi Farmaceutici S.p.A **Identifiers:** NCT00929851, CCD-0906-PR-0016, 2009-012546-23 (EudraCT Number)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout relatively high but even in both included groups (13% in beclomethasone dipropionate/formoterol and 16.9% in formoterol group)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Wedzicha 2016

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial **Duration:** 52 weeks **Location:** 43 countries, 496 centres

Participants	**Population** 1. indacaterol/glycopyrronium (1678) 2. salmeterol/fluticasone (1680) **Baseline characteristics:** age: 64.6 years (SD 7.8). Male/female: 2557/805. % predicted FEV1: 44.1% (SD 9.5%) **Inclusion criteria:** COPD % predicted FEV1 25%-60%, mMRC $\geq$ 2, with recent exacerbation **Exclusion criteria:** pregnancy, significant comorbidities, history of malignancy, LTOT, asthma, other concomitant lung disease, lung transplant
Interventions	1. Indacaterol/glycopyrronium (110/50 μg) once daily 2. Salmeterol/fluticasone (50/500 μg) twice daily **Inhaler device** 1. Indacaterol/glycopyrronium: DPI 2. Salmeterol/fluticasone: dry inhalation powder delivered via Accuhaler **Allowed co-medications:** salbutamol as rescue
Outcomes	**Primary:** rate of COPD exacerbations per year
Notes	**Funding:** Novartis **Identifiers:** NCT01782326, CQVA149A2318

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised via interactive response technology to 1 of the treatment arms
Allocation concealment (selection bias)	Low risk	Participants were randomised via interactive response technology to 1 of the treatment arms
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigator staff, assessors, and data analysts were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal was relatively low and even between 2 groups, 16.6% in indacaterol/ glycopyrronium arm and 19.0% in salmeterol/ fluticasone arm

Wedzicha 2016 (*Continued*)

Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

Wise 2013

Methods	**Design:** randomised, active-controlled, double-blind, double-dummy, parallel-group design, multicentre study **Duration:** 120 weeks **Location:** Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, Colombia, Croatia, Denmark, Finland, France, Georgia, Germany, Greece, Guatemala, Hungary, India, Ireland, Israel, Italy, Republic of Korea, Latvia, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Panama, Peru, Philippines, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, Ukraine, UK, USA
Participants	**Population** 1. Tiotropium inhalation solution 5 μg (5705) 2. Tiotropium inhalation capsules 18 μg (5687) **Baseline characteristics:** age 65.0 (SD 9.1) female:male 4879:12,237 **Inclusion criteria** 1. Signed informed consent consistent with International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines prior to participation in the trial, which includes medication washout and restrictions 2. Male or female patients $\geq$ 40 years 3. Current or ex-smokers with a smoking history of $\geq$ 10 pack-years. (Patients who have never smoked cigarettes excluded) 4. Diagnosis of COPD (P06-12085), 5. Relatively stable airway obstruction with a post-bronchodilator FEV1 $\leq$ 70% of predicted normal and post-bronchodilator FEV1/FVC $\leq$ 70% 6. Able to inhale from the HandiHaler® and the Respimat® devices **Exclusion criteria** 1. Significant diseases other than COPD. A significant disease is defined as a disease or condition which, in the opinion of the investigator, may put the participant at risk because of participation in the study or may influence the participant's ability to participate in the study 2. Recent history (i.e. $\leq$ 6 months) of MI 3. Unstable or life-threatening cardiac arrhythmia requiring intervention or change in drug therapy during the last year 4. Hospitalisation for cardiac failure (NYHA Class 3 or 4) during the past year 5. Known active TB 6. History of asthma, cystic fibrosis, clinically evident bronchiectasis, interstitial lung disease, or pulmonary thromboembolic disease 7. History of thoracotomy with pulmonary resection. 8. Malignancy for which the participant had undergone resection, radiation, chemotherapy or biological treatments within the last 5 years. Participants with treated basal cell carcinoma were allowed. 9. Known respiratory infection or exacerbation of COPD in the 4 weeks prior to

	randomisation. 10. Known narrow-angle glaucoma 11. Known significant symptomatic prostatic hyperplasia or bladder-neck obstruction. Participants whose symptoms were controlled on treatment may have been included. 12. Use of systemic corticosteroid medication at unstable doses (i.e. < 6 weeks on stable dose) or at doses > the equivalent of 10 mg prednisolone/d 13. Using supplemental oxygen therapy for > 12 h/d
Interventions	**Inhaler device** 1. Tiotropium inhalation solution delivered by the Respimat Inhaler 2. Tiotropium inhalation capsules delivered by the HandiHaler **Allowed co-medications:** as-needed salbutamol/albuterol. All classes of maintenance respiratory medications
Outcomes	**Primary:** mortality, COPD exacerbations
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01126437

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Interactive voice- or web-response system
Allocation concealment (selection bias)	Low risk	Interactive voice- or web-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Scientific Steering Committee met every 6 months to review both the progress and blinded study data
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was high but even in both included groups (23.2% in tiotropium 5 μg and 23.0% in tiotropium 18 μg group)
Selective reporting (reporting bias)	Low risk	Located trial registration and protocol - outcomes well reported

Yao 2014

Methods	**Design:** multicentre, randomised, double-blind, placebo-controlled, parallel-group study **Duration:** 26 weeks **Location:** Hong Kong, India, Japan, Republic of Korea, Singapore, Taiwan
Participants	**Population** 1. Indacaterol 150 μg (187) 2. Indacaterol 300 μg (188) **Baseline characteristics:** age 66.7 (SD 8.38) female:male 12:335 **Inclusion criteria** Diagnosis of moderate-severe COPD, as classified by the GOLD criteria and: 1. Smoking history of at least 20 pack-years 2. Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value 3. Post-bronchodilator FEV1/FVC < 70% **Exclusion criteria** 1. Hospitalised for a COPD exacerbation in the 6 weeks prior to screening or during the 14-day run-in period prior to randomisation 2. LTOT (> 15 h/d) for chronic hypoxaemia 3. Respiratory tract infection within 6 weeks prior to screening 4. Concomitant pulmonary disease 5. History of asthma 6. Diabetes type 1 or uncontrolled diabetes type 2 7. Lung cancer or a history of lung cancer 8. Active cancer or a history of cancer with < 5 years disease-free survival time 9. History of long QT syndrome or whose QTc interval (Bazett's) measured at screening or randomisation is prolonged 10. Vaccinated with live attenuated vaccines within 30 days prior to screening or during the run-in period 11. Unable to successfully use a DPI device or perform spirometry measurements
Interventions	**Inhaler device:** indacaterol was supplied in powder-filled capsules with a single-dose DPI **Allowed co-medications:** salbutamol as rescue. ICSs and slow-release theophylline
Outcomes	**Primary:** trough FEV1 24 h post-dose at the end of treatment (week 12 + 1 day, day 85)
Notes	**Funding:** Novartis **Identifiers:** NCT00794157, CQAB149B2333

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, no specific details but industry-funded
Allocation concealment (selection bias)	Unclear risk	No details

Yao 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was low and even between included arms (8.8% in indacaterol 150 μg and 9.4% in indacaterol 300 μg arm)
Selective reporting (reporting bias)	Low risk	Located trial registration - outcomes well reported

Zhong 2015

Methods	**Design:** randomised, double-blind, parallel-group, double-dummy, placebo-controlled trial **Duration:** 26 weeks **Location:** 4 countries and 56 centres (recruited mainly in China)
Participants	**Population** 1. Indacaterol/glycopyrronium (372) 2. Fluticasone propionate/salmeterol (369) **Baseline characteristics** Age: indacaterol/glycopyrronium 64.8 years (SD 7.8); fluticasone propionate/salmeterol 65.3 years (SD 7.9) Male/female: 672/69 % predicted FEV1: indacaterol/glycopyrronium 51.6% (SD 12.8%), fluticasone propionate/salmeterol 52.0% (SD 12.9%) **Inclusion criteria:** COPD stage 2/3; mMRC $\geq$ 2, without recent exacerbation **Exclusion criteria:** pregnancy, significant comorbidities, COPD exacerbations within the last year, LTOT (> 12 h/d), asthma, other concomitant lung disease
Interventions	1. Indacaterol/glycopyrronium (110/50 μg) once daily 2. Fluticasone propionate/salmeterol (500/50 μg) twice daily **Inhaler device:** 1. Indacaterol/glycopyrronium: DPI 2. Fluticasone propionate/salmeterol: dry inhalation powder delivered via Accuhaler **Allowed co-medications:** inhaled SABAs as rescue
Outcomes	**Primary:** trough FEV1 following 26 weeks of treatment to demonstrate the non-inferiority of indacaterol/glycopyrronium to fluticasone propionate/salmeterol
Notes	**Funding:** Novartis **Identifiers:** NCT01709903, CQVA149A2331

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised via interactive response technology to 1 of the treatment arms
Allocation concealment (selection bias)	Low risk	Participants were randomised via interactive response technology to 1 of the treatment arms
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants from the investigator staff, assessors, and data analysts was maintained by ensuring that the randomisation data were kept strictly confidential until the time of unblinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal was low and even between two groups, 7.8% in indacaterol/glycopyrronium arm and 10.4% in fluticasone propionate/salmeterol arm
Selective reporting (reporting bias)	Low risk	Study was registered and the prespecified outcomes were appropriately described

ZuWallack 2014a

Methods	**Design:** multicentre, randomised, double-blind, placebo-controlled, parallel-group trial **Duration:** 12 weeks **Location:** 90 centres across the USA
Participants	**Population:** 1132 adults, with a clinical history of moderate-severe COPD as defined by GOLD criteria (FEV1 < 80% and ≥ 30% predicted), were randomised to 1. Tiotropium + olodaterol (567) 2. Tiotropium + placebo (565) **Baseline characteristics:** mean age 64 years. 50% men. Mean FEV1 1.45 L (54% predicted) **Inclusion criteria:** men and women aged ≥ 40 years with a clinical diagnosis of COPD, a smoking history ≥ 10 pack-years, and post-bronchodilator FEV1 < 80% and ≥ 30% predicted, with FEV1/FVC < 70% **Exclusion criteria:** participants who were on prednisolone at an unstable dose (i.e. changed in < 6 weeks) or > 10 mg/day, oxygen use > 1 h/d, pulmonary rehabilitation in the last 6 weeks, participants who had significant disease other than COPD (e.g.

	asthma, history of life-threatening pulmonary obstruction, cystic fibrosis, clinically evident bronchiectasis, active TB, previous thoracotomy with resection, thyrotoxicosis, paroxysmal tachycardia, unstable or life-threatening cardiac arrhythmia, MI or hospitalisation for heart failure in the previous year, malignancy requiring treatment in the last 5 years)
Interventions	**Inhaler device** 1. Olodaterol 5 μg through DPI Respimat, once daily + tiotropium 18 μg through DPI HandiHaler, once daily 2. Placebo to olodaterol + tiotropium 18 μg through DPI HandiHaler, once daily **Allowed co-medications:** ICS, oral ($\leq$ 10 mg prednisone per day, or equivalent) and injected steroids, cromolyn sodium/nedocromil sodium, antihistamines, antileukotrienes, methylxanthines, mucolytics, and theophyllines were permitted. Albuterol as rescue
Outcomes	**Primary:** AUC for FEV1 measured 0-3 h post-morning dose after 12 weeks of treatment. Also trough FEV1 after 12 weeks of treatment **Secondary:** change in FEV1, SGRQ, FVC AUC 0-3 h, change in peak and trough FVC after 12 weeks' treatment, and rescue medication use over the 12-week period
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01694771

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An automated and validated randomisation tool (interactive response technologies) was used to randomise participants to each treatment arm, and to randomise the medication numbers on each kit to the different products
Allocation concealment (selection bias)	Low risk	An automated and validated randomisation tool (interactive response technologies) was used to randomise participants to each treatment arm, and to randomise the medication numbers on each kit to the different products
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors and data analysts were blinded to the identity of the treatment from the time of randomisation until database lock

ZuWallack 2014a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of withdrawals were relatively low and even in each group (40 participants in both groups, 7%)
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

ZuWallack 2014a&b

Methods	**Design:** multicentre, randomised, double-blind, placebo-controlled, parallel-group trial **Duration:** 12 weeks **Location:** 90 centres across the USA
Participants	**Population:** 2267 adults, with a clinical history of moderate-severe COPD as defined by GOLD criteria (FEV1 < 80% and ≥ 30% predicted), were randomised to 1. Tiotropium + olodaterol (1133) 2. Tiotropium + placebo (1134) **Baseline characteristics:** mean age 64 years. 50% men. Mean FEV1 1.45 L (54% predicted) **Inclusion criteria:** men and women aged ≥ 40 years with a clinical diagnosis of COPD, a smoking history ≥ 10 pack-years, and post-bronchodilator FEV1 < 80% and ≥ 30% predicted, with FEV1/FVC < 70% **Exclusion criteria:** participants who were on prednisolone at an unstable dose (i.e. changed in < 6 weeks) or > 10 mg/day, oxygen use > 1 h/d, pulmonary rehabilitation in the last 6 weeks, participants who had significant disease other than COPD (e.g. asthma, history of life-threatening pulmonary obstruction, cystic fibrosis, clinically evident bronchiectasis, active TB, previous thoracotomy with resection, thyrotoxicosis, paroxysmal tachycardia, unstable or life-threatening cardiac arrhythmia, MI or hospitalisation for heart failure in the previous year, malignancy requiring treatment in the last 5 years)
Interventions	**Inhaler device** 1. Olodaterol 5 μg through DPI Respimat, once daily + tiotropium 18 μg through DPI HandiHaler, once daily 2. Placebo to olodaterol + tiotropium 18 μg through DPI HandiHaler, once daily **Allowed co-medications:** ICS, oral (≤ 10 mg prednisone/d, or equivalent) and injected steroids, cromolyn sodium/nedocromil sodium, antihistamines, antileukotrienes, methylxanthines, mucolytics, and theophyllines were permitted. Albuterol as rescue
Outcomes	**Primary:** AUC for FEV1 measured 0-3 h post-morning dose after 12 weeks of treatment. Also trough FEV1 after 12 weeks of treatment **Secondary:** change in FEV1, SGRQ, FVC AUC 0-3 h, change in peak and trough FVC after 12 weeks' treatment, and rescue medication use over the 12-week period
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01694771, NCT01696058
Risk of bias	

ZuWallack 2014a&b *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An automated and validated randomisation tool (interactive response technologies) was used to randomise participants to each treatment arm, and to randomise the medication numbers on each kit to the different products
Allocation concealment (selection bias)	Low risk	An automated and validated randomisation tool (interactive response technologies) was used to randomise participants to each treatment arm, and to randomise the medication numbers on each kit to the different products
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors and data analysts were blinded to the identity of the treatment from the time of randomisation until database lock
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of withdrawals were relatively low and even in each group (See ZuWallack 2014a and ZuWallack 2014b)
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

ZuWallack 2014b

Methods	**Design:** multicentre, randomised, double-blind, placebo-controlled, parallel-group trial **Duration:** 12 weeks **Location:** 90 centres across the USA
Participants	**Population:** 1135 adults, with a clinical history of moderate-severe COPD as defined by GOLD criteria (FEV1 < 80% and ≥ 30% predicted), were randomised to 1. Tiotropium + olodaterol (566) 2. Tiotropium + placebo (569) **Baseline characteristics:** mean age 64 years. 50% men. Mean FEV1 1.45 L (54% predicted) **Inclusion criteria:** men and women aged ≥ 40 years with a clinical diagnosis of COPD, a smoking history ≥ 10 pack-years, and post-bronchodilator FEV1 < 80% and ≥ 30% predicted, with FEV1/FVC < 70% **Exclusion criteria:** participants who were on prednisolone at an unstable dose (i.e. changed in < 6 weeks) or > 10 mg/day, oxygen use > 1 h/d, pulmonary rehabilitation

	in the last 6 weeks, participants who had significant disease other than COPD (e.g. asthma, history of life-threatening pulmonary obstruction, cystic fibrosis, clinically evident bronchiectasis, active TB, previous thoracotomy with resection, thyrotoxicosis, paroxysmal tachycardia, unstable or life-threatening cardiac arrhythmia, MI or hospitalisation for heart failure in the previous year, malignancy requiring treatment in the last 5 years)
Interventions	**Inhaler device** 1. Olodaterol 5 μg through DPI Respimat, once daily + tiotropium 18 μg through DPI HandiHaler, once daily 2. Placebo to olodaterol + tiotropium 18 μg through DPI HandiHaler, once daily **Allowed co-medications:** ICS, oral (10 mg prednisone per day, or equivalent) and injected steroids, cromolyn sodium/nedocromil sodium, antihistamines, antileukotrienes, methylxanthines, mucolytics, and theophyllines were permitted. Albuterol as rescue
Outcomes	**Primary:** AUC for FEV1 measured 0-3 h post-morning dose after 12 weeks of treatment. Also trough FEV1 after 12 weeks of treatment **Secondary:** change in FEV1, SGRQ, FVC AUC 0-3 h, change in peak and trough FVC after 12 weeks' treatment, and rescue medication use over the 12-week period
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT01696058

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	An automated and validated randomisation tool (interactive response technologies) was used to randomise participants to each treatment arm, and to randomise the medication numbers on each kit to the different products
Allocation concealment (selection bias)	Low risk	An automated and validated randomisation tool (interactive response technologies) was used to randomise participants to each treatment arm, and to randomise the medication numbers on each kit to the different products
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	People performing the assessments and data analysts were blinded to the identity of the treatment from the time of randomisation until database lock

ZuWallack 2014b *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of withdrawals were relatively low and even in each group ((31/569; 5.5%) and 43/566; 7.5%))
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were reported in full

6MWD: 6-minute walk distance; **AEs:** adverse events; **ALT:** alanine transaminase; **AST:** aspartate transaminase; **ATS:** American Thoracic Society; **AUC:** area under curve; **BDI:** Baseline Dyspnea Index; **BiPAP:** bilevel positive airway pressure; **BMI:** body mass index; **BODE:** body-mass index, airflow obstruction, dyspnoea, and exercise; **BPH:** benign prostatic hypertrophy; **BPM:** beats per minute; **CAT:** Chronic obstructive pulmonary disease Assessment Test; **CBSQ:** Chronic Bronchitis Symptom Questionnaire; **CFB:** change from baseline; **COPD:** chronic obstructive pulmonary disease; **CPAP:** continuous positive airway pressure; **CRDQ:** Chronic Respiratory Disease Questionnaire; **CT:** computed tomography; **CVD:** cardiovascular disease; **DPI:** dry powder inhaler; **ECG:** electrocardiogram; **ER:** emergency room; **ERS:** European Respiratory Society; **FDC:** fixed-dose combination; **FEV1:** forced expiratory volume in 1 second; **FF:** fluticasone furoate; **FP:** fluticasone propionate; **FVC:** forced vital capacity; **GOLD:** Global Initiative for Chronic Obstructive Lung Disease; **ICS:** inhaled corticosteroids; **IRT:** interactive response technology ; **ITT:** intention to treat; **LABA:** long-acting beta-adrenoceptor agonist; **LAMA:** long-acting muscarinic antagonist; **LTOT:** long term oxygen therapy; **LVRS:** lung volume reduction surgery; **MCID:** minimal clinically important difference; **MDI:** metered-dose inhaler; **MI:** myocardial infarction; modified; **mMRC:** modified Medical Research Council; **NHANES:** National Health and Nutrition Examination Survey; **NYHA:** New York Heart Association; **OCS:** oral corticosteroids; **PDE4:** phosphodiesterase 4; **PEF:** peak expiratory flow; **PI:** principal investigator; **pred:** predicted; **QoL:** quality of life; **QTc:** corrected QT interval; **SABA:** short-acting beta2-adrenergic agonist **SAL:** salmeterol; **SD:** standard deviation; **SGOT:** serum glutamic-oxaloacetic transaminase; **SGPT:** serum glutamate pyruvate transaminase; **SGRQ:** St George's Respiratory Questionnaire; **TB:** tuberculosis; **TDI:** Transition Dyspnea Index; **TIA:** transient ischaemic attack; **ULN:** upper limit of normal; **VI:** vilanterol

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
1237.20	2-week study
1237.4	4-week study
1237.7	Cross-over study
Bateman 2010	No qualified comparison (formulation and/or dose not approved)
Beeh 2014	Cross-over study
Beeh 2016	Cross-over study
Berton 2016	3-week cross-over study
Celli 2014	No qualified comparison (formulation and/or dose not approved)

(*Continued*)

CQAB149BIL01	No qualified comparison (indacaterol vs LABA)
CQMF149F2202	No qualified comparison (formulation and/or dose not approved)
D'Urzo 2013	No qualified comparison (formulation and/or dose not approved)
Dahl 2013	4-week study
Donohue 2014	No qualified comparison (formulation and/or dose not approved)
Donohue 2016b	Cross-over study
Dransfield 2013	No qualified comparison (formulation and/or dose not approved)
Fang 2008	Poor-quality study (dropout rate too high)
Ferguson 2014	No qualified comparison (formulation and/or dose not approved)
Gelb 2013	No qualified comparison (formulation and/or dose not approved)
HZC113108	No qualified comparison (formulation and/or dose not approved)
Jones 1997	No qualified comparison (formulation and/or dose not approved)
Jones 2012	No qualified comparison (formulation and/or dose not approved)
Kerwin 2012b	No qualified comparison (formulation and/or dose not approved)
Kerwin 2013	No qualified comparison (formulation and/or dose not approved)
Kurashima 2009	Cross-over study
Lipson 2018	Results were not available at the time of data extraction
Magnussen 2012	8-week study
Mahler 2014	6-week study
Mahmud 2007	COPD not defined. Insufficient data
Make 2014	Abstract only. Insufficient information
Maltais 2014a	Cross-over study
Maltais 2014b	Cross-over study
Maltais 2018	No qualified comparison (formulation and/or dose not approved)

(*Continued*)

Martinez 2013	No qualified comparison (formulation and/or dose not approved)
MORACTO1	6-week study
MORACTO2	6-week study
PT003016-00	No comparator, 4-week study
Rabe 2008	6-week study
Rennard 2013	No qualified comparison (formulation and/or dose not approved)
Rossi 2012	6-week study
SCO100646	Cross-over study
Siler 2017	No qualified comparison (formulation and/or dose not approved)
Singh 2016	Cross-over study
Tashkin 2016	7-day cross-over study
To 2011	Insufficient data. Abstract only
Van Noord 2010	6-week study
Vestbo 2016	Did not meet inclusion criteria (fluticasone furorate/vilanterol compared with existing maintenance treatment)
Vogelmeier 2010a	No qualified comparison (dose not approved)
Vogelmeier 2010b	14-day study
Vogelmeier 2013b	Spin-off of Vogelmeier 2011
Watz 2016	Cross-over study
Wouters 2005	Did not meet inclusion criteria
Zheng 2015	No qualified comparison (formulation and/or dose not approved)

COPD: chronic obstructive pulmonary disease; **LABA:** long-acting beta-adrenoceptor agonist

Characteristics of studies awaiting assessment *[ordered by study ID]*

Calverley 2018

Methods	**Design:** randomised, double-blind, active-controlled parallel-group study **Duration:** 52 weeks **Location:** Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Czechia, Denmark, Finland, France, Germany, Greece, Guatemala, Hong Kong, Hungary, India, Ireland, Italy, Japan, Republic of Korea, Latvia, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Romania, Russian Federation, Serbia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, UK, USA, Vietnam
Participants	**Population** 1. Tiotropium 5 μg (3941) 2. Tiotropium 5 μg + olodaterol 5 μg (3939) **Baseline characteristics:** mean age 66.4 (SD 8.5); female:male 2254:5626 (28.6%:71.4%). Mean post-bronchodilator FEV1 1.18 L **Inclusion criteria** 1. Male or female patients, $\geq$ 40 years of age 2. Diagnosis of COPD with a documented post-bronchodilator FEV1 < 60% of predicted normal and a post-bronchodilator FEV1/FVC < 70% at visit 1 3. Documented history of at least 1 moderate-severe COPD exacerbation in the previous 12 months requiring treatment with systemic corticosteroids and/or antibiotics and/or related hospitalisation 4. Symptomatically stable as defined by: no evidence of COPD exacerbation requiring use of either antibiotics and/or steroids 4 weeks prior to visit 1 and no evidence of change in their usual COPD medication 4 weeks prior to visit 1 5. Current or ex-smokers with a smoking history of > 10 pack-years **Exclusion criteria** 1. Significant disease other than COPD 2. Unstable COPD requiring oral steroids, phosphodiesterase 4 inhibitor, oral or patch beta-adrenergics 3. Pregnancy
Interventions	**Inhaler device** 1. Tiotropium + olodaterol high-dose, FDC. Once daily 2 puffs solution for inhalation Respimat 2. Tiotropium. Once daily 2 puffs solution for inhalation Respimat **Allowed co-medications:** salbutamol as rescue. ICSs
Outcomes	**Primary:** annualised rate of moderate-severe COPD exacerbations during the actual treatment period. (time frame: from first intake of study medication until 1 day after last intake of study medication, up to 361 days). Annualised rate of moderate-severe COPD exacerbations during the actual treatment period was calculated per treatment per patient—year. The actual treatment period was defined as the interval from first intake of study medication until 1 day after last intake of study medication
Notes	**Funding:** Boehringer Ingelheim **Identifiers:** NCT02296138

Papi 2017

Methods	**Design:** a multicentre, randomised, double-blind, active-controlled, parallel-group study **Duration:** 52 weeks **Location:** Bulgaria, Germany, Hungary, Republic of Korea, Latvia, Lithuania, Macedonia, the former Yugoslav, Poland, Romania, Russian Federation, Slovakia, South Africa, Spain, Ukraine, and UK
Participants	**Population** 1. Fluticasone/formoterol (Flutiform) 500 μg/20μg (587) 2. Fluticasone/formoterol (Flutiform) 250 μg/20μg (588) 3. Formoterol 500 μg/20μg (590) **Baseline characteristics:** average age 63-64, male/female 0.75:0.25 **Inclusion criteria:** 1. Male or female participants aged $\geq$ 40 years at screening visit 2. Smoking history of $\geq$ 10 pack-years. 3. Diagnosis of COPD 4. History of $\geq$ moderate or severe COPD exacerbations in previous year 5. Willing and able to replace current COPD therapy with study medication 6. Able to demonstrate correct use of a pressurised MDI without a spacer 7. Willing and able to attend all study visits and complete study assessments 8. Able to provide signed informed consent **Exclusion criteria** 1. Ongoing moderate or severe exacerbation of COPD 2. Current diagnosis of asthma 3. Documented evidence of α1-antitrypsin deficiency as the underlying cause of COPD 4. Other active respiratory disease such as active TB, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung disease, cystic fibrosis, bronchiolitis obliterans 5. Previous lung resection 6. Use of LTOT at least 12 h daily or mechanical ventilation 7. Chest X-ray or CT scan that reveals evidence of clinically significant abnormalities reflective of active disease not believed to be due to COPD 8. Evidence of uncontrolled CVD 9. Evidence of clinically significant renal, hepatic, gastrointestinal, or psychiatric disease 10. Current malignancy or a previous history of cancer that has been in remission for < 5 years (basal cell or squamous cell carcinoma of the skin which has been resected is not excluded) 11. Clinically significant sleep apnoea requiring use of CPAP device or non-invasive positive pressure ventilation device 12. Participation in the acute phase of a pulmonary rehabilitation programme within 4 weeks prior to screening or during the study 13. Known or suspected history of drug or alcohol abuse in the last 2 years 14. Requiring treatment with any of the prohibited concomitant medications 15. Known or suspected hypersensitivity or contraindication to any of the study drugs or excipients 16. Received an investigational drug within 30 days of the screening visit (12 weeks if an oral or injectable steroid)
Interventions	**Inhaler device** 1. Fluticasone/formoterol 250/10 µg Flutiform (2 puffs twice daily) 2. Fluticasone/formoterol 125/5 µg Flutiform (2 puffs twice daily) 3. Formoterol 12 µg (1 puff twice daily) **Allowed co-medications:** SABA as rescue
Outcomes	Annual rate of moderate and severe COPD exacerbations (time frame: 52 weeks)

Notes	**Funding:** Mundipharma Research Limited **Identifiers:** NCT01946620

COPD: chronic obstructive pulmonary disease; **CPAP:** continuous positive airway pressure; **CT:** computed tomography; **CVD:** cardiovascular disease; **FDC:** fixed dose combination; **FEV1:** forced expiratory volume in 1 second; **FVC:** forced vital capacity; **LTOT:** long-term oxygen therapy; **MDI:** metered dose inhaler

Characteristics of ongoing studies *[ordered by study ID]*

AMPLIFY

Trial name or title	A 24 week treatment, multicentre, randomized, double blinded, double dummy, parallel-group, clinical trial evaluating the efficacy and safety of aclidinium bromide 400 μg/formoterol fumarate 12 μg fixed-dose combination bid compared with each monotherapy (aclidinium bromide 400 μg bid and formoterol fumarate 12 μg bid) and tiotropium 18 μg qd when administered to patients with stable chronic obstructive pulmonary disease
Methods	Interventional (clinical study)
Participants	1595 participants
Interventions	1. Aclidinium/formoterol 2. Aclidinium 3. Formoterol 4. Tiotropium 5. Placebo
Outcomes	1. CFB in 1-h morning post-dose FEV1 of aclidinium bromide/formoterol fumarate 400 μg/12 μg compared to AB 400 μg at week 24. (time frame: baseline 1-h post-dose and week 24) 2. CFB in morning pre-dose (trough) FEV1 of aclidinium bromide/formoterol fumarate 400 μg/12 μg compared to formoterol fumarate 12 μg at week 24. (time frame: baseline morning pre-dose and week 24) 3. CFB in morning pre-dose (trough) FEV1 at week 24 comparing aclidinium bromide 400 μg versus tiotropium 18 μg to demonstrate non-inferiority (time frame: baseline morning pre-dose and week 24)
Starting date	5 July 2016
Contact information	AstraZeneca
Notes	NCT02796677

AVANT

Trial name or title	A 24-week treatment, randomised, parallel-group, double blinded, double-dummy, multicentre study to assess the efficacy and safety of aclidinium bromide/formoterol fumarate compared with individual components and placebo and aclidinium bromide compared with placebo when administered to patients with stable chronic obstructive pulmonary disease
Methods	Interventional (clinical study)
Participants	1060 participants
Interventions	1. Aclidinium/formoterol 2. Aclidinium 3. Formoterol 4. Tiotropium 5. Placebo
Outcomes	1. CFB in 1-h morning post-dose FEV1 (time frame: week 24) 2. CFB in morning pre-dose (trough) FEV1 (time frame: week 24) 3. CFB in trough FEV1 (time frame: week 24)
Starting date	24 January 2017
Contact information	AstraZeneca
Notes	NCT03022097

FLASH

Trial name or title	A 12-week treatment, multicentre, randomized, double-blind, double-dummy, parallel group study to assess the efficacy and safety of switching from salmeterol/fluticasone to QVA149 (indacaterol maleate/glycopyrronium bromide) in symptomatic COPD patients
Methods	Interventional (clinical study)
Participants	492 participants
Interventions	1. Indacaterol/glycopyrronium 2. Fluticasone propionate/salmeterol
Outcomes	1. CFB in trough pre-dose FEV1 in both arms (time frame: week 12)
Starting date	6 August 2015
Contact information	Novartis Pharmaceuticals +41613241111
Notes	NCT02516592

FLT3510

Trial name or title	A randomised double-blind, double-dummy parallel group study to compare the efficacy and safety of fluticasone propionate/formoterol fumarate (Flutiform®) 500 μg/20 µg bid and 250 μg/10 µg bid versus salmeterol/fluticasone (Seretide®) 50 μg/500 µg bid in participants with chronic obstructive pulmonary disease (COPD)
Methods	Interventional (clinical study)
Participants	923 participants
Interventions	1. Fluticasone propionate/formoterol fumarate 500 μg/20 µg twice daily and 250 μg/10 µg twice daily 2. Salmeterol/fluticasone 50 μg/500 µg twice daily
Outcomes	1. Average pre-dose FEV1 (time frame: 26 weeks)
Starting date	September 2014
Contact information	Mundipharma Research Limited
Notes	NCT02195375

PINNACLE 4

Trial name or title	A randomized, double-blind, chronic dosing (24 weeks), placebo-controlled, parallel group, multicentre study to assess the efficacy and safety of PT003, PT005, and PT001 in participants with moderate to very severe COPD, compared with placebo
Methods	Interventional (clinical study)
Participants	1759 participants
Interventions	1. Glycopyrronium/formoterol 2. Glycopyrronium 3. Formoterol 4. Placebo
Outcomes	1. CFB in morning pre-dose trough FEV1 of treatment (time frame: at week 24)
Starting date	30 March 2015
Contact information	Pearl Therapeutics
Notes	NCT02343458

PT010006

Trial name or title	A randomized, double-blind, parallel-group, 24-week, chronic-dosing, multicentre study to assess the efficacy and safety of PT010, PT003, and PT009 compared with Symbicort® Turbuhaler® as an active control in participants with moderate to very severe chronic obstructive pulmonary disease
Methods	Interventional (clinical study)
Participants	1800 participants
Interventions	1. Glycopyrronium/formoterol 2. Budesonide/formoterol 3. Budesonide/formoterol
Outcomes	1. CFB in morning pre-dose trough FEV1 (time frame: 24 weeks)
Starting date	10 August 2015
Contact information	Pearl Therapeutics
Notes	NCT02497001

CFB: change from baseline; **FEV1:** forced expiratory volume in 1 second

DATA AND ANALYSES

Comparison 1. LABA/LAMA vs LABA/ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Moderate to severe exacerbations	7	7687	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.74, 1.00]
1.1 High-risk	1	3372	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.76, 1.00]
1.2 Low-risk	6	4315	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.65, 1.14]
2 Severe exacerbations	5	6214	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.46, 1.27]
2.1 High-risk	1	3354	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.74, 1.06]
2.2 Low-risk	4	2860	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.27, 1.63]
3 SGRQ responders at 3 months	4	2397	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.92, 1.27]
3.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Low-risk	4	2397	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.92, 1.27]
4 SGRQ responders at 6 months	1	427	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.88, 1.89]
4.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Low-risk	1	427	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.88, 1.89]
5 SGRQ responders at 12 months	1	3195	Odds Ratio (M-H, Random, 95% CI)	1.25 [1.09, 1.43]
5.1 HIgh-risk	1	3195	Odds Ratio (M-H, Random, 95% CI)	1.25 [1.09, 1.43]
5.2 Low-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Change from baseline in SGRQ at 3 months	6	6342	Mean Difference (IV, Random, 95% CI)	-0.49 [-1.41, 0.43]
6.1 High-risk	1	3195	Mean Difference (IV, Random, 95% CI)	-1.30 [-2.35, -0.25]
6.2 Low-risk	5	3147	Mean Difference (IV, Random, 95% CI)	-0.03 [-1.02, 0.96]
7 Change from baseline in SGRQ at 6 months	3	4360	Mean Difference (IV, Random, 95% CI)	-1.18 [-2.20, -0.16]
7.1 High-risk	1	3195	Mean Difference (IV, Random, 95% CI)	-1.20 [-2.28, -0.12]
7.2 Low-risk	2	1165	Mean Difference (IV, Random, 95% CI)	-0.99 [-4.12, 2.14]
8 Change from baseline in SGRQ at 12 months	1	3195	Mean Difference (IV, Random, 95% CI)	-1.20 [-2.34, -0.06]
8.1 High-risk	1	3195	Mean Difference (IV, Random, 95% CI)	-1.20 [-2.34, -0.06]
8.2 Low-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9 TDI at 3 months	6	4152	Mean Difference (IV, Random, 95% CI)	0.40 [0.02, 0.78]
9.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Low-risk	6	4152	Mean Difference (IV, Random, 95% CI)	0.40 [0.02, 0.78]
10 TDI at 6 months	3	1780	Mean Difference (IV, Random, 95% CI)	0.13 [-0.24, 0.51]
10.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Low-risk	3	1780	Mean Difference (IV, Random, 95% CI)	0.13 [-0.24, 0.51]
11 Change from baseline in FEV1 at 3 months	7	6466	Mean Difference (IV, Random, 95% CI)	0.08 [0.04, 0.11]
11.1 High-risk	1	3192	Mean Difference (IV, Random, 95% CI)	0.08 [0.06, 0.10]
11.2 Low-risk	6	3274	Mean Difference (IV, Random, 95% CI)	0.08 [0.03, 0.12]
12 Change from baseline in FEV1 at 6 months	4	5292	Mean Difference (IV, Random, 95% CI)	0.09 [0.07, 0.11]
12.1 High-risk	1	3192	Mean Difference (IV, Random, 95% CI)	0.09 [0.07, 0.11]
12.2 Low-risk	3	2100	Mean Difference (IV, Random, 95% CI)	0.10 [0.05, 0.15]
13 Change from baseline in FEV1 at 12 months	1	3192	Mean Difference (IV, Random, 95% CI)	0.06 [0.04, 0.08]

13.1 High-risk	1	3192	Mean Difference (IV, Random, 95% CI)	0.06 [0.04, 0.08]
13.2 Low-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14 Mortality	9	8796	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.61, 1.68]
14.1 High-risk	1	3358	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.57, 1.77]
14.2 Low-risk	8	5438	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.35, 3.23]
15 Total SAE	9	8796	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.75, 1.07]
15.1 High-risk	1	3358	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.76, 1.08]
15.2 Low-risk	8	5438	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.22]
16 COPD SAE	9	8796	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.54, 1.27]
16.1 High-risk	1	3358	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.70, 1.07]
16.2 Low-risk	8	5438	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.39, 1.64]
17 Cardiac SAE	9	8796	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.61, 1.24]
17.1 High-risk	1	3358	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.58, 1.29]
17.2 Low-risk	8	5438	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.43, 1.89]
18 Dropouts due to adverse events	9	8796	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.74, 1.07]
18.1 High-risk	1	3358	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.13]
18.2 Low-risk	8	5438	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.68, 1.19]
19 Pneumonia	8	8753	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.39, 0.84]
19.1 High-risk	1	3358	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.40, 0.96]
19.2 Low-risk	7	5395	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.19, 0.97]

Comparison 2. LABA/LAMA vs LAMA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Moderate to severe exacerbations	9	7398	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.75, 1.23]
1.1 High-risk	1	2206	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.89, 1.27]
1.2 Low-risk	8	5192	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.66, 1.30]
2 Severe exacerbations	8	5241	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.59, 1.36]
2.1 High-risk	1	304	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.45, 1.16]
2.2 Low-risk	7	4937	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.57, 1.72]
3 SGRQ responders at 3 months	9	4490	Odds Ratio (M-H, Random, 95% CI)	1.32 [1.16, 1.51]
3.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Low-risk	9	4490	Odds Ratio (M-H, Random, 95% CI)	1.32 [1.16, 1.51]
4 SGRQ responders at 6 months	10	10255	Odds Ratio (M-H, Random, 95% CI)	1.26 [1.17, 1.37]
4.1 High-risk	1	2019	Odds Ratio (M-H, Random, 95% CI)	1.30 [1.08, 1.56]
4.2 Low-risk	9	8236	Odds Ratio (M-H, Random, 95% CI)	1.26 [1.15, 1.37]
5 SGRQ responders at 12 months	2	4015	Odds Ratio (M-H, Random, 95% CI)	1.19 [1.04, 1.35]
5.1 High-risk	1	1743	Odds Ratio (M-H, Random, 95% CI)	1.27 [1.04, 1.55]
5.2 Low-risk	1	2272	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.95, 1.34]
6 Change from baseline in SGRQ at 3 months	12	10259	Mean Difference (IV, Random, 95% CI)	-1.74 [-2.31, -1.18]
6.1 High-risk	1	2064	Mean Difference (IV, Random, 95% CI)	-3.68 [-5.84, -1.52]
6.2 Low-risk	11	8195	Mean Difference (IV, Random, 95% CI)	-1.60 [-2.19, -1.01]
7 Change from baseline in SGRQ at 6 months	11	9217	Mean Difference (IV, Random, 95% CI)	-1.31 [-1.93, -0.70]
7.1 High-risk	1	2019	Mean Difference (IV, Random, 95% CI)	-2.79 [-5.02, -0.56]
7.2 Low-risk	10	7198	Mean Difference (IV, Random, 95% CI)	-1.20 [-1.83, -0.57]

8 Change from baseline in SGRQ at 12 months	5	6000	Mean Difference (IV, Random, 95% CI)	-1.15 [-2.24, -0.06]
8.1 High-risk	1	2206	Mean Difference (IV, Random, 95% CI)	-3.38 [-5.83, -0.93]
8.2 Low-risk	4	3794	Mean Difference (IV, Random, 95% CI)	-0.87 [-1.64, -0.10]
9 TDI at 3 months	10	7027	Mean Difference (IV, Random, 95% CI)	0.48 [0.34, 0.62]
9.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Low-risk	10	7027	Mean Difference (IV, Random, 95% CI)	0.48 [0.34, 0.62]
10 TDI at 6 months	7	6099	Mean Difference (IV, Random, 95% CI)	0.32 [0.17, 0.46]
10.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Low-risk	7	6099	Mean Difference (IV, Random, 95% CI)	0.32 [0.17, 0.46]
11 TDI at 12 months	4	5257	Mean Difference (IV, Random, 95% CI)	0.21 [0.10, 0.33]
11.1 High-risk	1	304	Mean Difference (IV, Random, 95% CI)	-0.38 [-1.28, 0.52]
11.2 Low-risk	3	4953	Mean Difference (IV, Random, 95% CI)	0.22 [0.11, 0.34]
12 Change from baseline in FEV1 at 3 months	18	12891	Mean Difference (IV, Random, 95% CI)	0.07 [0.06, 0.08]
12.1 High-risk	1	1982	Mean Difference (IV, Random, 95% CI)	0.06 [0.02, 0.09]
12.2 Low-risk	17	10909	Mean Difference (IV, Random, 95% CI)	0.07 [0.06, 0.09]
13 Change from baseline in FEV1 at 6 months	14	11002	Mean Difference (IV, Random, 95% CI)	0.06 [0.05, 0.07]
13.1 High-risk	1	1780	Mean Difference (IV, Random, 95% CI)	0.06 [0.02, 0.10]
13.2 Low-risk	13	9222	Mean Difference (IV, Random, 95% CI)	0.06 [0.05, 0.07]
14 Change from baseline in FEV1 at 12 months	7	8072	Mean Difference (IV, Random, 95% CI)	0.06 [0.04, 0.08]
14.1 High-risk	1	2206	Mean Difference (IV, Random, 95% CI)	0.05 [0.01, 0.09]
14.2 Low-risk	6	5866	Mean Difference (IV, Random, 95% CI)	0.06 [0.04, 0.08]
15 Mortality	24	20683	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.75, 1.36]
15.1 High-risk	2	2510	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.66, 1.69]
15.2 Low-risk	22	18173	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.66, 1.43]
16 Total SAE	25	21453	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.92, 1.12]
16.1 High-risk	2	2510	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.80, 1.20]
16.2 Low-risk	23	18943	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.91, 1.16]
17 COPD SAE	22	20101	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.17]
17.1 High-risk	1	2206	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.84, 1.39]
17.2 Low-risk	21	17895	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.79, 1.17]
18 Cardiac SAE	22	20736	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.78, 1.25]
18.1 High-risk	1	2206	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.53, 1.20]
18.2 Low-risk	21	18530	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.82, 1.45]
19 Dropouts due to adverse events	26	21877	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.96, 1.27]
19.1 High-risk	2	2510	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.75, 1.41]
19.2 Low-risk	24	19367	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.96, 1.31]
20 Pneumonia	24	21048	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.83, 1.53]
20.1 High-risk	2	2510	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.59, 1.61]
20.2 Low-risk	22	18538	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.84, 1.81]

Comparison 3. LABA/LAMA vs LABA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Moderate to severe exacerbations	5	2488	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.62, 0.97]
1.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Low-risk	5	2488	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.62, 0.97]
2 Severe exacerbations	6	2898	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.55, 1.12]
2.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Low-risk	6	2898	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.55, 1.12]
3 SGRQ responders at 6 months	6	5870	Odds Ratio (M-H, Random, 95% CI)	1.30 [1.10, 1.53]
3.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Low-risk	6	5870	Odds Ratio (M-H, Random, 95% CI)	1.30 [1.10, 1.53]
4 SGRQ responders at 12 months	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 High-risk	0		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Low-risk	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Change from baseline in SGRQ at 3 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 High-risk	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Low-risk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Change from baseline in SGRQ at 6 months	5	3649	Mean Difference (IV, Random, 95% CI)	-1.09 [-1.96, -0.22]
6.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Low-risk	5	3649	Mean Difference (IV, Random, 95% CI)	-1.09 [-1.96, -0.22]
7 Change from baseline in SGRQ at 12 months	2	2507	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.64, 0.25]
7.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Low-risk	2	2507	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.64, 0.25]
8 TDI at 3 months	3	3342	Mean Difference (IV, Random, 95% CI)	0.52 [0.31, 0.74]
8.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Low-risk	3	3342	Mean Difference (IV, Random, 95% CI)	0.52 [0.31, 0.74]
9 TDI at 6 months	4	4126	Mean Difference (IV, Random, 95% CI)	0.40 [0.23, 0.57]
9.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Low-risk	4	4126	Mean Difference (IV, Random, 95% CI)	0.40 [0.23, 0.57]
10 TDI at 12 months	3	4516	Mean Difference (IV, Random, 95% CI)	0.42 [0.06, 0.77]
10.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Low-risk	3	4516	Mean Difference (IV, Random, 95% CI)	0.42 [0.06, 0.77]
11 Change from baseline in FEV1 at 3 months	4	2469	Mean Difference (IV, Random, 95% CI)	0.07 [0.03, 0.12]
11.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Low-risk	4	2469	Mean Difference (IV, Random, 95% CI)	0.07 [0.03, 0.12]
12 Change from baseline in FEV1 at 6 months	8	6144	Mean Difference (IV, Random, 95% CI)	0.07 [0.06, 0.08]
12.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Low-risk	8	6144	Mean Difference (IV, Random, 95% CI)	0.07 [0.06, 0.08]
13 Change from baseline in FEV1 at 12 months	6	5063	Mean Difference (IV, Random, 95% CI)	0.07 [0.06, 0.09]
13.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 Low-risk	6	5063	Mean Difference (IV, Random, 95% CI)	0.07 [0.06, 0.09]
14 Mortality	10	7930	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.68, 2.09]

14.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Low-risk	10	7930	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.68, 2.09]
15 Total SAE	11	8699	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.91, 1.22]
15.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 Low-risk	11	8699	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.91, 1.22]
16 COPD SAE	8	7068	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.83, 1.40]
16.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 Low-risk	8	7068	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.83, 1.40]
17 Cardiac SAE	11	8699	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.69, 2.07]
17.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 Low-risk	11	8699	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.69, 2.07]
18 Dropouts due to adverse events	13	9202	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.68, 1.29]
18.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18.2 Low-risk	13	9202	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.68, 1.29]
19 Pneumonia	10	8252	Odds Ratio (M-H, Random, 95% CI)	1.54 [0.95, 2.49]
19.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19.2 Low-risk	10	8252	Odds Ratio (M-H, Random, 95% CI)	1.54 [0.95, 2.49]

Comparison 4. LABA/ICS vs LAMA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Moderate to severe exacerbations	3	2203	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.88, 1.34]
1.1 high-risk	2	1580	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.90, 1.39]
1.2 Low-risk	1	623	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.24, 1.66]
2 Severe exacerbations	3	2203	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.97, 1.63]
2.1 High-risk	2	1580	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.96, 1.61]
2.2 Low-risk	1	623	Risk Ratio (M-H, Random, 95% CI)	3.03 [0.32, 28.96]
3 SGRQ responders at 3 months	2	823	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.89, 1.55]
3.1 High-risk	1	214	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.56, 1.65]
3.2 Low-risk	1	609	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.92, 1.74]
4 SGRQ responders at 6 months	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 High-risk	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Low-risk	0		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 SGRQ responders at 12 months	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 High-risk	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Low-risk	0		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 SGRQ responder at 2 years	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 High-risk	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Low-risk	0		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Change from baseline in SGRQ at 3 months	3	814	Mean Difference (IV, Random, 95% CI)	-1.37 [-3.04, 0.30]
7.1 High-risk	1	214	Mean Difference (IV, Random, 95% CI)	-1.06 [-4.39, 2.27]
7.2 Low-risk	2	600	Mean Difference (IV, Random, 95% CI)	-1.48 [-3.41, 0.45]
8 Change from baseline in SGRQ at 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8.1 High-risk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Low-risk	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

9 Change from baseline in SGRQ at 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.1 High-risk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Low-risk	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10 Change from baseline in SGRQ at 2 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.1 High-risk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Low-risk	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 TDI at 3 months	2	1323	Mean Difference (IV, Random, 95% CI)	0.50 [0.20, 0.81]
11.1 High-risk	1	1198	Mean Difference (IV, Random, 95% CI)	0.50 [0.18, 0.82]
11.2 Low-risk	1	125	Mean Difference (IV, Random, 95% CI)	0.51 [-0.39, 1.41]
12 TDI at 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.1 High-risk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Low-risk	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 TDI at 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.1 High-risk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 Low-risk	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14 TDI at 2 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
14.1 High-risk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Low-risk	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
15 Change from baseline in FEV1 at 3 months	8	2379	Mean Difference (IV, Random, 95% CI)	0.02 [-0.02, 0.05]
15.1 High-risk	2	1353	Mean Difference (IV, Random, 95% CI)	0.01 [-0.02, 0.04]
15.2 Low-risk	6	1026	Mean Difference (IV, Random, 95% CI)	0.02 [-0.02, 0.06]
16 Change from baseline in FEV1 at 6 months	2	1301	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.02]
16.1 High-risk	1	1071	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.02]
16.2 Low-risk	1	230	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.06, 0.06]
17 Change from baseline in FEV1 at 12 months	2	933	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.08, 0.05]
17.1 High-risk	2	933	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.08, 0.05]
17.2 Low-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
18 Change from baseline in FEV1 at 2 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
18.1 High-risk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
18.2 Low-risk	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
19 Mortality	5	2395	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.31, 0.88]
19.1 High-risk	2	1580	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.31, 0.90]
19.2 Low-risk	3	815	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.06, 3.82]
20 Total SAE	5	2590	Odds Ratio (M-H, Random, 95% CI)	1.25 [1.00, 1.55]
20.1 High-risk	2	1580	Odds Ratio (M-H, Random, 95% CI)	1.29 [1.03, 1.63]
20.2 Low-risk	3	1010	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.49, 1.77]
21 COPD SAE	5	2590	Odds Ratio (M-H, Random, 95% CI)	1.33 [0.99, 1.78]
21.1 High-risk	2	1580	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.33, 2.96]
21.2 Low-risk	3	1010	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.21, 4.99]
22 Cardiac SAE	3	2208	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.34, 1.08]
22.1 High-risk	1	1323	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.39, 1.15]
22.2 Low-risk	2	885	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.02, 1.34]
23 Dropouts due to adverse events	6	2657	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.73, 1.34]
23.1 High-risk	2	1580	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.74, 1.47]
23.2 Low-risk	4	1077	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.35, 1.71]
24 Pneumonia	4	2465	Odds Ratio (M-H, Random, 95% CI)	1.93 [1.15, 3.23]

24.1 High-risk	2	1580	Odds Ratio (M-H, Random, 95% CI)	1.80 [1.06, 3.06]
24.2 Low-risk	2	885	Odds Ratio (M-H, Random, 95% CI)	5.82 [0.70, 48.80]

Comparison 5. LABA/ICS vs LABA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Moderate to severe exacerbations	16	15730	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.77, 0.89]
1.1 High-risk	10	9041	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.75, 0.89]
1.2 Low-risk	6	6689	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
2 Severe exacerbations	11	10698	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.14]
2.1 High-risk	5	4216	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.74, 1.13]
2.2 Low-risk	6	6482	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.90, 1.24]
3 SGRQ responders at 3 months	2	1427	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.73, 1.11]
3.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Low-risk	2	1427	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.73, 1.11]
4 SGRQ responders at 6 months	4	4618	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.96, 1.22]
4.1 High-risk	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Low-risk	4	4618	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.96, 1.22]
5 SGRQ responders at 12 months	4	4349	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.95, 1.60]
5.1 High-risk	3	2337	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.78, 1.72]
5.2 Low-risk	1	2012	Odds Ratio (M-H, Random, 95% CI)	1.42 [1.18, 1.70]
6 SGRQ responders at 3 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 High-risk	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Low-risk	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Change from baseline in SGRQ at 3 months	4	3602	Mean Difference (IV, Random, 95% CI)	-1.53 [-2.48, -0.58]
7.1 High-risk	3	2552	Mean Difference (IV, Random, 95% CI)	-1.81 [-2.99, -0.64]
7.2 Low-risk	1	1050	Mean Difference (IV, Random, 95% CI)	-1.00 [-2.61, 0.61]
8 Change from baseline in SGRQ at 6 months	9	7857	Mean Difference (IV, Random, 95% CI)	-1.32 [-1.94, -0.70]
8.1 High-risk	5	3687	Mean Difference (IV, Random, 95% CI)	-1.40 [-2.53, -0.26]
8.2 Low-risk	4	4170	Mean Difference (IV, Random, 95% CI)	-1.18 [-1.97, -0.40]
9 Change from baseline in SGRQ at 12 months	9	8322	Mean Difference (IV, Random, 95% CI)	-1.75 [-2.44, -1.06]
9.1 High-risk	8	6605	Mean Difference (IV, Random, 95% CI)	-1.75 [-2.61, -0.89]
9.2 Low-risk	1	1717	Mean Difference (IV, Random, 95% CI)	-1.70 [-2.82, -0.58]
10 Change from baseline in SGRQ at 3 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.1 High-risk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Low-risk	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 TDI at 3 months	4	1968	Mean Difference (IV, Random, 95% CI)	0.13 [-0.26, 0.52]
11.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Low-risk	4	1968	Mean Difference (IV, Random, 95% CI)	0.13 [-0.26, 0.52]
12 TDI at 6 months	4	1917	Mean Difference (IV, Random, 95% CI)	0.21 [-0.09, 0.50]
12.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Low-risk	4	1917	Mean Difference (IV, Random, 95% CI)	0.21 [-0.09, 0.50]

13 Change from baseline in FEV1 at 3 months	12	7829	Mean Difference (IV, Random, 95% CI)	0.05 [0.04, 0.06]
13.1 High-risk	5	4435	Mean Difference (IV, Random, 95% CI)	0.05 [0.03, 0.07]
13.2 Low-risk	7	3394	Mean Difference (IV, Random, 95% CI)	0.05 [0.04, 0.06]
14 Change from baseline in FEV1 at 6 months	11	6555	Mean Difference (IV, Random, 95% CI)	0.04 [0.03, 0.06]
14.1 High-risk	7	4560	Mean Difference (IV, Random, 95% CI)	0.05 [0.03, 0.07]
14.2 Low-risk	4	1995	Mean Difference (IV, Random, 95% CI)	0.04 [0.01, 0.07]
15 Change from baseline in FEV1 at 12 months	8	4628	Mean Difference (IV, Random, 95% CI)	0.05 [0.03, 0.07]
15.1 High-risk	8	4628	Mean Difference (IV, Random, 95% CI)	0.05 [0.03, 0.07]
15.2 Low-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16 Change from baseline in FEV1 at 3 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
16.1 High-risk	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 Low-risk	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17 Mortality	21	19681	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.11]
17.1 High-risk	15	12976	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.69, 1.30]
17.2 Low-risk	6	6705	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.76, 1.15]
18 Total SAE	20	19204	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.13]
18.1 High-risk	14	12499	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.89, 1.09]
18.2 Low-risk	6	6705	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.92, 1.47]
19 COPD SAE	17	16397	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.83, 1.04]
19.1 High-risk	11	9692	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.07]
19.2 Low-risk	6	6705	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.12]
20 Cardiac SAE	17	17085	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.77, 1.27]
20.1 High-risk	11	10380	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.68, 1.38]
20.2 Low-risk	6	6705	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.21]
21 Dropouts due to adverse events	21	19713	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.80, 0.98]
21.1 High-risk	15	13008	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.77, 1.00]
21.2 Low-risk	6	6705	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.77, 1.06]
22 Pneumonia	20	19291	Odds Ratio (M-H, Random, 95% CI)	1.48 [1.14, 1.92]
22.1 High-risk	14	12586	Odds Ratio (M-H, Random, 95% CI)	1.46 [1.03, 2.08]
22.2 Low-risk	6	6705	Odds Ratio (M-H, Random, 95% CI)	1.64 [1.25, 2.14]

Comparison 6. LAMA vs LABA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Moderate to severe exacerbations	6	11943	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.79, 0.93]
1.1 High-risk	1	7376	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.76, 0.92]
1.2 Low-risk	5	4567	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.79, 1.07]
2 Severe exacerbations	5	10696	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.53, 1.10]
2.1 High-risk	1	7376	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.78, 1.01]
2.2 Low-risk	4	3320	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.36, 1.13]
3 SGRQ responders at 3 months	2	4495	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.13]
3.1 High-risk	1	2999	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.84, 1.12]
3.2 Low-risk	1	1496	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.59, 0.89]
4 SGRQ responders at 6 months	8	11831	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.92, 1.15]

4.1 High-risk	1	2829	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.93, 1.25]
4.2 Low-risk	7	9002	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.89, 1.16]
5 SGRQ responders at 12 months	2	4709	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.15]
5.1 High-risk	1	2587	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.17]
5.2 Low-risk	1	2122	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.88, 1.26]
6 Change from baseline in SGRQ at 3 months	4	7191	Mean Difference (IV, Random, 95% CI)	1.13 [-0.09, 2.34]
6.1 High-risk	1	3019	Mean Difference (IV, Random, 95% CI)	0.10 [-0.82, 1.02]
6.2 Low-risk	3	4172	Mean Difference (IV, Random, 95% CI)	1.84 [0.87, 2.80]
7 Change from baseline in SGRQ at 6 months	7	7972	Mean Difference (IV, Random, 95% CI)	-0.39 [-1.03, 0.25]
7.1 High-risk	1	2848	Mean Difference (IV, Random, 95% CI)	-0.70 [-1.74, 0.34]
7.2 Low-risk	6	5124	Mean Difference (IV, Random, 95% CI)	-0.25 [-1.09, 0.58]
8 Change from baseline in SGRQ at 12 months	3	5397	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.79, 0.62]
8.1 High-risk	1	2606	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.56, 0.76]
8.2 Low-risk	2	2791	Mean Difference (IV, Random, 95% CI)	0.10 [-0.79, 0.99]
9 TDI at 3 months	4	7881	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.37, 0.09]
9.1 High-risk	1	3024	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.15, -0.13]
9.2 Low-risk	3	4857	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.63, 0.27]
10 TDI at 6 months	5	7444	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.24, 0.01]
10.1 High-risk	1	2863	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.20, -0.18]
10.2 Low-risk	4	4581	Mean Difference (IV, Random, 95% CI)	0.00 [-0.17, 0.18]
11 TDI at 12 months	4	7421	Mean Difference (IV, Random, 95% CI)	0.02 [-0.25, 0.29]
11.1 High-risk	1	2610	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.27, -0.25]
11.2 Low-risk	3	4811	Mean Difference (IV, Random, 95% CI)	0.15 [-0.11, 0.40]
12 Change from baseline in FEV1 at 3 months	8	5420	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.02, 0.02]
12.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Low-risk	8	5420	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.02, 0.02]
13 Change from baseline in FEV1 at 6 months	10	7770	Mean Difference (IV, Random, 95% CI)	0.02 [0.00, 0.03]
13.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 Low-risk	10	7770	Mean Difference (IV, Random, 95% CI)	0.02 [0.00, 0.03]
14 Change from baseline in FEV1 at 12 months	5	5353	Mean Difference (IV, Random, 95% CI)	0.02 [0.01, 0.03]
14.1 High-risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Low-risk	5	5353	Mean Difference (IV, Random, 95% CI)	0.02 [0.01, 0.03]
15 Mortality	13	22844	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.75, 1.24]
15.1 High-risk	2	10815	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.66, 1.16]
15.2 Low-risk	11	12029	Odds Ratio (M-H, Random, 95% CI)	1.33 [0.79, 2.25]
16 Total SAE	14	23191	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.87, 1.02]
16.1 High-risk	2	10815	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
16.2 Low-risk	12	12376	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.88, 1.15]
17 COPD SAE	12	22136	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.71, 1.04]
17.1 High-risk	2	10815	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.69, 0.91]
17.2 Low-risk	10	11321	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.65, 1.27]
18 Cardiac SAE	12	22153	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.91, 1.38]
18.1 High-risk	2	10815	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.83, 1.44]
18.2 Low-risk	10	11338	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.83, 1.61]
19 Dropuouts due to adverse events	14	22755	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.78, 1.02]

19.1 High-risk	2	10815	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.05]
19.2 Low-risk	12	11940	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.72, 1.10]
20 Pneumonia	12	22153	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.68, 1.13]
20.1 High-risk	2	10815	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.61, 1.13]
20.2 Low-risk	10	11338	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.61, 1.69]

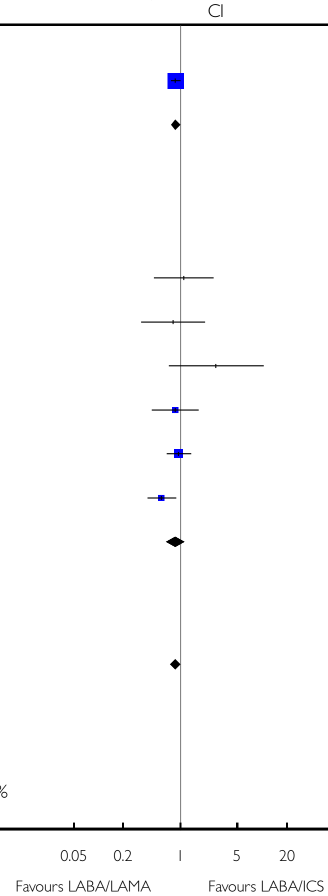
Analysis 1.1. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 1 Moderate to severe exacerbations.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 1 Moderate to severe exacerbations

Study or subgroup	LABA/LAMA n/N	LABA/ICS n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2016	686/1675	751/1697		59.1 %	0.87 [0.76, 1.00]
Subtotal (95% CI)	**1675**	**1697**		**59.1 %**	**0.87 [0.76, 1.00]**
Total events: 686 (LABA/LAMA), 751 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.94 (P = 0.053)					
2 Low-risk					
Donohue 2015a	12/353	11/353		3.2 %	1.09 [0.48, 2.51]
Donohue 2015b	9/349	11/348		2.8 %	0.81 [0.33, 1.98]
Singh 2015c	8/358	3/358		1.3 %	2.70 [0.71, 10.28]
Vogelmeier 2013a	18/258	21/264		5.1 %	0.87 [0.45, 1.67]
Vogelmeier 2016	74/467	77/466		16.3 %	0.95 [0.67, 1.35]
Zhong 2015	44/372	68/369		12.2 %	0.59 [0.39, 0.89]
Subtotal (95% CI)	**2157**	**2158**		**40.9 %**	**0.86 [0.65, 1.14]**
Total events: 165 (LABA/LAMA), 191 (LABA/ICS)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 6.59$, df = 5 (P = 0.25); $I^2 = 24\%$					
Test for overall effect: Z = 1.06 (P = 0.29)					
Total (95% CI)	**3832**	**3855**		**100.0 %**	**0.86 [0.74, 1.00]**
Total events: 851 (LABA/LAMA), 942 (LABA/ICS)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.67$, df = 6 (P = 0.35); $I^2 = 10\%$					
Test for overall effect: Z = 1.92 (P = 0.054)					
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.91), $I^2 = 0.0\%$					



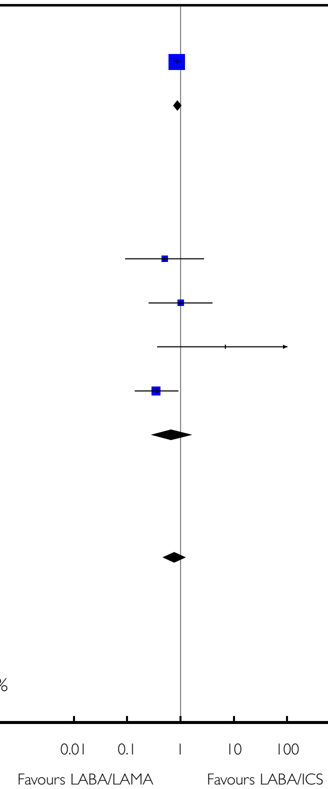
Analysis 1.2. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 2 Severe exacerbations.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 2 Severe exacerbations

Study or subgroup	LABA/LAMA n/N	LABA/ICS n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2016	259/1675	288/1679		58.3 %	0.88 [0.74, 1.06]
Subtotal (95% CI)	**1675**	**1679**		**58.3 %**	**0.88 [0.74, 1.06]**
Total events: 259 (LABA/LAMA), 288 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.32 (P = 0.19)					
2 Low-risk					
Donohue 2015a	2/353	4/353		7.9 %	0.50 [0.09, 2.73]
Donohue 2015b	4/349	4/348		11.1 %	1.00 [0.25, 4.02]
Singh 2015c	3/358	0/358		2.8 %	7.06 [0.36, 137.16]
Zhong 2015	6/372	16/369		19.9 %	0.36 [0.14, 0.93]
Subtotal (95% CI)	**1432**	**1428**		**41.7 %**	**0.66 [0.27, 1.63]**
Total events: 15 (LABA/LAMA), 24 (LABA/ICS)					
Heterogeneity: Tau^2 = 0.27; Chi^2 = 4.34, df = 3 (P = 0.23); I^2 =31%					
Test for overall effect: Z = 0.90 (P = 0.37)					
Total (95% CI)	**3107**	**3107**		**100.0 %**	**0.76 [0.46, 1.27]**
Total events: 274 (LABA/LAMA), 312 (LABA/ICS)					
Heterogeneity: Tau^2 = 0.11; Chi^2 = 5.65, df = 4 (P = 0.23); I^2 =29%					
Test for overall effect: Z = 1.05 (P = 0.29)					
Test for subgroup differences: Chi^2 = 0.39, df = 1 (P = 0.53), I^2 =0.0%					



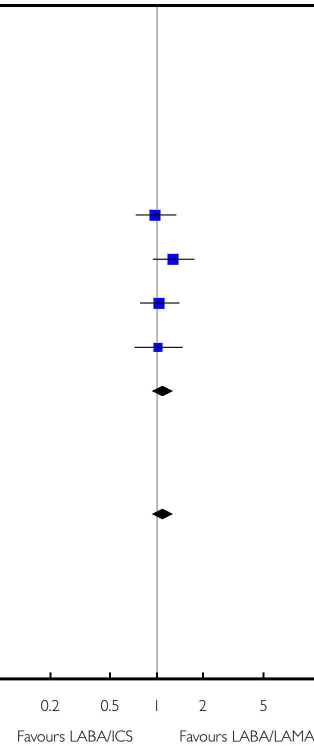
Analysis 1.3. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 3 SGRQ responders at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 3 SGRQ responders at 3 months

Study or subgroup	LABA/LAMA n/N	LABA/ICS n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low-risk					
Donohue 2015a	171/315	173/316		26.2 %	0.98 [0.72, 1.34]
Donohue 2015b	169/322	143/309		26.3 %	1.28 [0.94, 1.75]
Singh 2015c	168/330	168/337		27.9 %	1.04 [0.77, 1.41]
Vogelmeier 2013a	116/230	119/238		19.6 %	1.02 [0.71, 1.46]
Subtotal (95% CI)	**1197**	**1200**		**100.0 %**	**1.08 [0.92, 1.27]**
Total events: 624 (LABA/LAMA), 603 (LABA/ICS)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.67, df = 3 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 0.93 (P = 0.35)					
Total (95% CI)	**1197**	**1200**		**100.0 %**	**1.08 [0.92, 1.27]**
Total events: 624 (LABA/LAMA), 603 (LABA/ICS)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.67, df = 3 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 0.93 (P = 0.35)					
Test for subgroup differences: Not applicable					



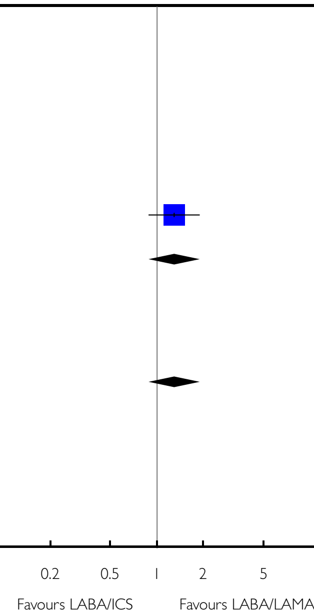
Analysis 1.4. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 4 SGRQ responders at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 4 SGRQ responders at 6 months

Study or subgroup	LABA/LAMA n/N	LABA/ICS n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low-risk					
Vogelmeier 2013a	117/211	106/216		100.0 %	1.29 [0.88, 1.89]
Subtotal (95% CI)	**211**	**216**		**100.0 %**	**1.29 [0.88, 1.89]**
Total events: 117 (LABA/LAMA), 106 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.32 (P = 0.19)					
Total (95% CI)	**211**	**216**		**100.0 %**	**1.29 [0.88, 1.89]**
Total events: 117 (LABA/LAMA), 106 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.32 (P = 0.19)					
Test for subgroup differences: Not applicable					



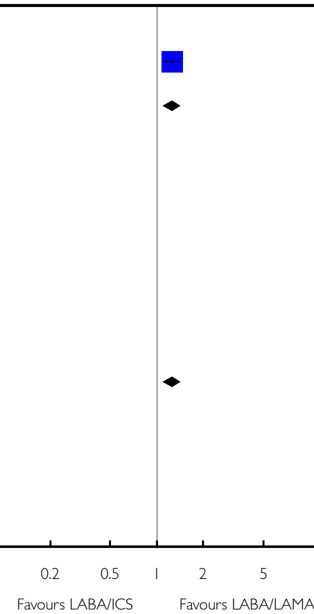
Analysis 1.5. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 5 SGRQ responders at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 5 SGRQ responders at 12 months

Study or subgroup	LABA/LAMA n/N	LABA/ICS n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 HIgh-risk					
Wedzicha 2016	788/1602	696/1593		100.0 %	1.25 [1.09, 1.43]
Subtotal (95% CI)	**1602**	**1593**		**100.0 %**	**1.25 [1.09, 1.43]**
Total events: 788 (LABA/LAMA), 696 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.11 (P = 0.0018)					
2 Low-risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**1602**	**1593**		**100.0 %**	**1.25 [1.09, 1.43]**
Total events: 788 (LABA/LAMA), 696 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.11 (P = 0.0018)					
Test for subgroup differences: Not applicable					



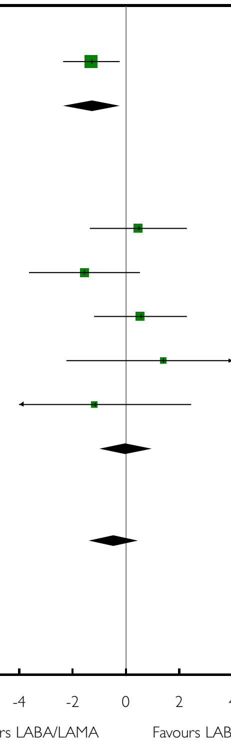
Analysis 1.6. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 6 Change from baseline in SGRQ at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 6 Change from baseline in SGRQ at 3 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA/ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2016	1593	-3.2 (15.17)	1602	-1.9 (15.21)		35.1 %	-1.30 [-2.35, -0.25]
Subtotal (95% CI)	**1593**		**1602**			**35.1 %**	**-1.30 [-2.35, -0.25]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.42 (P = 0.016)							
2 Low-risk							
Donohue 2015a	312	-6.33 (11.62)	313	-6.79 (11.59)		18.3 %	0.46 [-1.36, 2.28]
Donohue 2015b	321	-7.23 (13.29)	307	-5.67 (13.18)		15.1 %	-1.56 [-3.63, 0.51]
Singh 2015c	329	-5.1 (11.35)	336	-5.64 (11.35)		19.8 %	0.54 [-1.19, 2.27]
Vogelmeier 2013a	242	-5.43 (20.55)	246	-6.83 (20.45)		5.8 %	1.40 [-2.24, 5.04]
Zhong 2015	372	-7.18 (25.17)	369	-6 (24.99)		5.9 %	-1.18 [-4.79, 2.43]
Subtotal (95% CI)	**1576**		**1571**			**64.9 %**	**-0.03 [-1.02, 0.96]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.78$, df = 4 (P = 0.44); I^2 =0.0%							
Test for overall effect: Z = 0.05 (P = 0.96)							
Total (95% CI)	**3169**		**3173**			**100.0 %**	**-0.49 [-1.41, 0.43]**
Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 6.76$, df = 5 (P = 0.24); I^2 =26%							
Test for overall effect: Z = 1.04 (P = 0.30)							
Test for subgroup differences: $Chi^2 = 2.98$, df = 1 (P = 0.08), I^2 =66%							



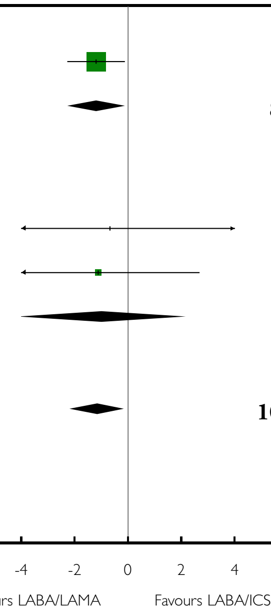
Analysis 1.7. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 7 Change from baseline in SGRQ at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 7 Change from baseline in SGRQ at 6 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA/ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2016	1602	-3.5 (15.61)	1593	-2.3 (15.57)		89.3 %	-1.20 [-2.28, -0.12]
Subtotal (95% CI)	**1602**		**1593**			**89.3 %**	**-1.20 [-2.28, -0.12]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.18 (P = 0.030)							
2 Low-risk							
Vogelmeier 2013a	231	-6.42 (30.56)	238	-5.72 (29.9)		3.5 %	-0.70 [-6.17, 4.77]
Zhong 2015	354	-7.51 (25.93)	342	-6.38 (25.39)		7.2 %	-1.13 [-4.94, 2.68]
Subtotal (95% CI)	**585**		**580**			**10.7 %**	**-0.99 [-4.12, 2.14]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.90); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.62 (P = 0.54)							
Total (95% CI)	**2187**		**2173**			**100.0 %**	**-1.18 [-2.20, -0.16]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.03$, df = 2 (P = 0.98); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.26 (P = 0.024)							
Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.90), $I^2 = 0.0\%$							



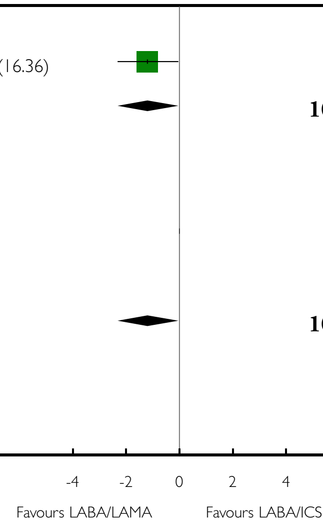
Analysis 1.8. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 8 Change from baseline in SGRQ at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 8 Change from baseline in SGRQ at 12 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA/ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2016	1602	-3.1 (16.41)	1593	-1.9 (16.36)		100.0 %	-1.20 [-2.34, -0.06]
Subtotal (95% CI)	**1602**		**1593**			**100.0 %**	**-1.20 [-2.34, -0.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.07 (P = 0.038)							
2 Low-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**1602**		**1593**			**100.0 %**	**-1.20 [-2.34, -0.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.07 (P = 0.038)							
Test for subgroup differences: Not applicable							



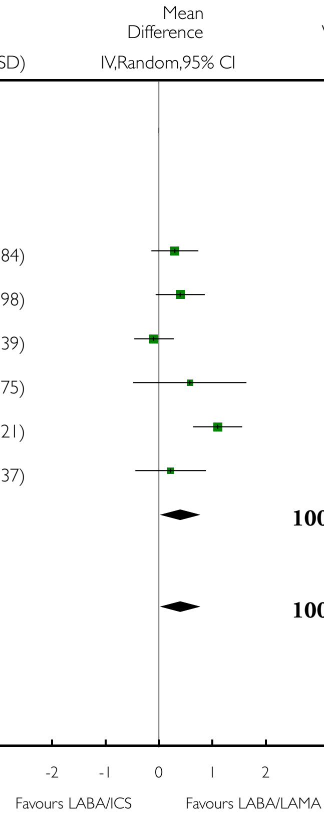
Analysis 1.9. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 9 TDI at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 9 TDI at 3 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA/ICS N	Mean(SD)	Weight	Mean Difference IV,Random,95% CI
1 High-risk						
Subtotal (95% CI)	**0**		**0**			**Not estimable**
Heterogeneity: not applicable						
Test for overall effect: not applicable						
2 Low-risk						
Donohue 2015a	309	3.3 (2.81)	316	3 (2.84)	19.0 %	0.30 [-0.14, 0.74]
Donohue 2015b	323	3 (2.88)	307	2.6 (2.98)	18.7 %	0.40 [-0.06, 0.86]
Singh 2015c	334	2 (2.56)	338	2.1 (2.39)	20.5 %	-0.10 [-0.47, 0.27]
Vogelmeier 2013a	224	2.03 (5.81)	236	1.45 (5.75)	8.6 %	0.58 [-0.48, 1.64]
Vogelmeier 2017	811	1.949 (3.54)	269	0.85 (3.21)	18.8 %	1.10 [0.64, 1.55]
Zhong 2015	348	2.62 (4.48)	337	2.4 (4.37)	14.4 %	0.22 [-0.44, 0.88]
Subtotal (95% CI)	**2349**		**1803**		**100.0 %**	**0.40 [0.02, 0.78]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 16.37$, df = 5 (P = 0.01); I^2 =69%						
Test for overall effect: Z = 2.05 (P = 0.041)						
Total (95% CI)	**2349**		**1803**		**100.0 %**	**0.40 [0.02, 0.78]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 16.37$, df = 5 (P = 0.01); I^2 =69%						
Test for overall effect: Z = 2.05 (P = 0.041)						
Test for subgroup differences: Not applicable						



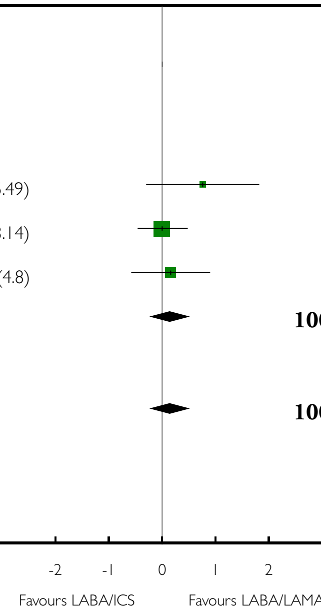
Analysis 1.10. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 10 TDI at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 10 TDI at 6 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA/ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Vogelmeier 2013a	212	2.36 (5.65)	213	1.6 (5.49)		12.3 %	0.76 [-0.30, 1.82]
Vogelmeier 2016	353	1.9 (3.19)	341	1.9 (3.14)		62.3 %	0.0 [-0.47, 0.47]
Zhong 2015	335	3.02 (4.87)	326	2.86 (4.8)		25.4 %	0.16 [-0.58, 0.90]
Subtotal (95% CI)	**900**		**880**			**100.0 %**	**0.13 [-0.24, 0.51]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.66$, df = 2 (P = 0.44); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.71 (P = 0.48)							
Total (95% CI)	**900**		**880**			**100.0 %**	**0.13 [-0.24, 0.51]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.66$, df = 2 (P = 0.44); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.71 (P = 0.48)							
Test for subgroup differences: Not applicable							



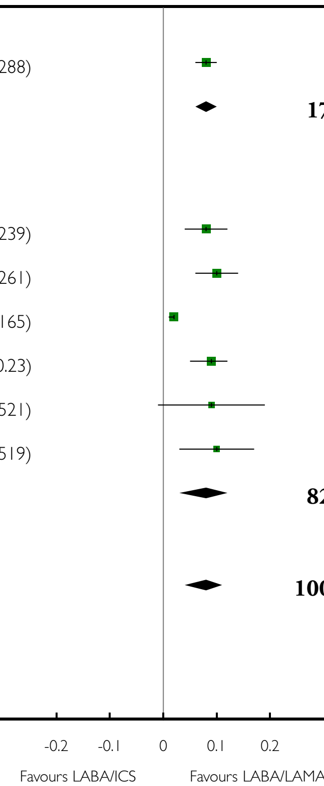
Analysis 1.11. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 11 Change from baseline in FEV1 at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 11 Change from baseline in FEV1 at 3 months

Study or subgroup	LABA/LAMA N	LABA/LAMA Mean(SD)	LABA/ICS N	LABA/ICS Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2016	1597	0.07 (0.288)	1595	-0.01 (0.288)		17.3 %	0.08 [0.06, 0.10]
Subtotal (95% CI)	**1597**		**1595**			**17.3 %**	**0.08 [0.06, 0.10]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.65 (P < 0.00001)							
2 Low-risk							
Donohue 2015a	312	0.154 (0.235)	317	0.07 (0.239)		15.4 %	0.08 [0.04, 0.12]
Donohue 2015b	349	0.185 (0.258)	348	0.09 (0.261)		15.2 %	0.10 [0.06, 0.14]
Hoshino 2015	22	0.214 (0.0123)	21	0.2 (0.0165)		18.1 %	0.02 [0.01, 0.02]
Singh 2015c	333	0.151 (0.23)	338	0.06 (0.23)		15.7 %	0.09 [0.05, 0.12]
Vogelmeier 2013a	258	0.29 (0.626)	235	0.2 (0.521)		7.6 %	0.09 [-0.01, 0.19]
Zhong 2015	372	0.183 (0.482)	369	0.08 (0.519)		10.7 %	0.10 [0.03, 0.17]
Subtotal (95% CI)	**1646**		**1628**			**82.7 %**	**0.08 [0.03, 0.12]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 45.27$, df = 5 (P<0.00001); I^2 =89%							
Test for overall effect: Z = 3.40 (P = 0.00067)							
Total (95% CI)	**3243**		**3223**			**100.0 %**	**0.08 [0.04, 0.11]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 66.03$, df = 6 (P<0.00001); I^2 =91%							
Test for overall effect: Z = 4.05 (P = 0.000051)							
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.92), I^2 =0.0%							



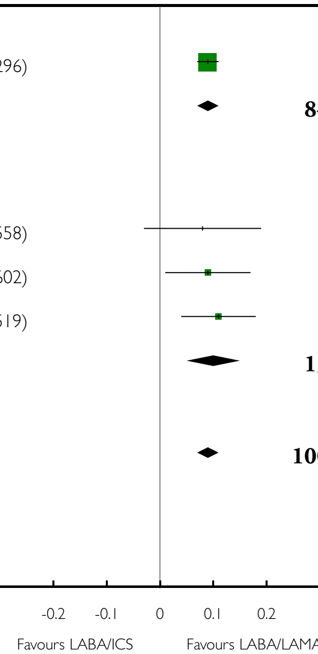
Analysis 1.12. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 12 Change from baseline in FEV1 at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 12 Change from baseline in FEV1 at 6 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA/ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2016	1597	0.049 (0.292)	1595	-0.04 (0.296)		84.8 %	0.09 [0.07, 0.11]
Subtotal (95% CI)	**1597**		**1595**			**84.8 %**	**0.09 [0.07, 0.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 8.26 (P < 0.00001)							
2 Low-risk							
Vogelmeier 2013a	212	0.24 (0.641)	216	0.16 (0.558)		2.7 %	0.08 [-0.03, 0.19]
Vogelmeier 2016	468	0.27 (0.627)	463	0.18 (0.602)		5.7 %	0.09 [0.01, 0.17]
Zhong 2015	372	0.163 (0.482)	369	0.05 (0.519)		6.8 %	0.11 [0.04, 0.18]
Subtotal (95% CI)	**1052**		**1048**			**15.2 %**	**0.10 [0.05, 0.15]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.26$, df = 2 (P = 0.88); I^2 =0.0%							
Test for overall effect: Z = 3.97 (P = 0.000073)							
Total (95% CI)	**2649**		**2643**			**100.0 %**	**0.09 [0.07, 0.11]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.45$, df = 3 (P = 0.93); I^2 =0.0%							
Test for overall effect: Z = 9.15 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.19$, df = 1 (P = 0.66), I^2 =0.0%							



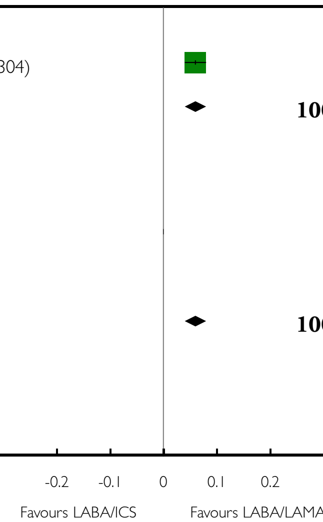
Analysis 1.13. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 13 Change from baseline in FEV1 at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 13 Change from baseline in FEV1 at 12 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA/ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2016	1597	0.015 (0.3)	1595	-0.05 (0.304)		100.0 %	0.06 [0.04, 0.08]
Subtotal (95% CI)	**1597**		**1595**			**100.0 %**	**0.06 [0.04, 0.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.89 (P < 0.00001)							
2 Low-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**1597**		**1595**			**100.0 %**	**0.06 [0.04, 0.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.89 (P < 0.00001)							
Test for subgroup differences: Not applicable							



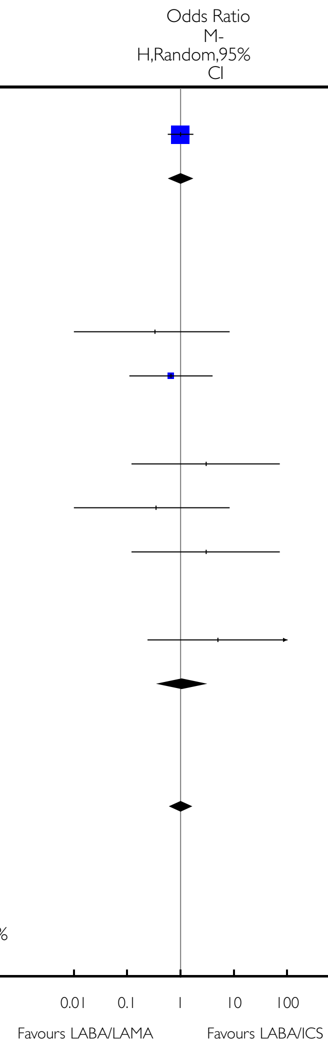
Analysis 1.14. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 14 Mortality.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 14 Mortality

Study or subgroup	LABA/LAMA n/N	LABA/ICS n/N	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk				
Wedzicha 2016	24/1678	24/1680	79.2 %	1.00 [0.57, 1.77]
Subtotal (95% CI)	**1678**	**1680**	**79.2 %**	**1.00 [0.57, 1.77]**
Total events: 24 (LABA/LAMA), 24 (LABA/ICS)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.00 (P = 1.0)				
2 Low-risk				
Donohue 2015a	0/353	1/353	2.5 %	0.33 [0.01, 8.19]
Donohue 2015b	2/349	3/348	8.0 %	0.66 [0.11, 3.99]
Hoshino 2015	0/22	0/21		Not estimable
Singh 2015c	1/358	0/358	2.5 %	3.01 [0.12, 74.10]
Vogelmeier 2013a	0/258	1/264	2.5 %	0.34 [0.01, 8.38]
Vogelmeier 2016	1/467	0/466	2.5 %	3.00 [0.12, 73.83]
Vogelmeier 2017	0/811	0/269		Not estimable
Zhong 2015	2/372	0/369	2.8 %	4.99 [0.24, 104.22]
Subtotal (95% CI)	**2990**	**2448**	**20.8 %**	**1.06 [0.35, 3.23]**
Total events: 6 (LABA/LAMA), 5 (LABA/ICS)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.07$, df = 5 (P = 0.69); I^2 =0.0%				
Test for overall effect: Z = 0.11 (P = 0.92)				
Total (95% CI)	**4668**	**4128**	**100.0 %**	**1.01 [0.61, 1.68]**
Total events: 30 (LABA/LAMA), 29 (LABA/ICS)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.07$, df = 6 (P = 0.80); I^2 =0.0%				
Test for overall effect: Z = 0.05 (P = 0.96)				
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.93), I^2 =0.0%				



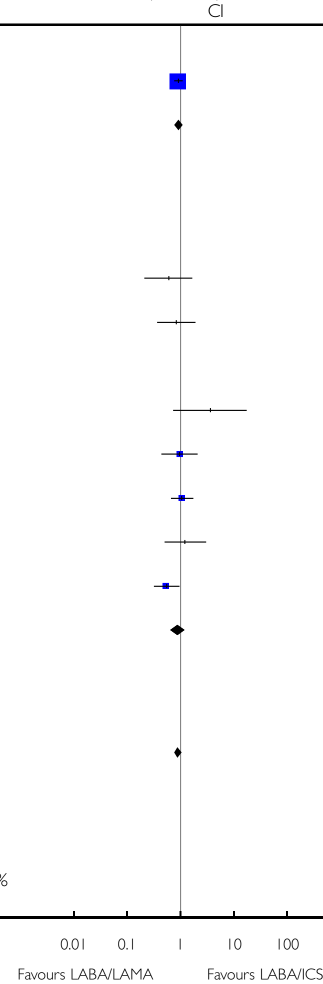
Analysis 1.15. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 15 Total SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 15 Total SAE

Study or subgroup	LABA/LAMA n/N	LABA/ICS n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2016	308/1678	334/1680		60.8 %	0.91 [0.76, 1.08]
Subtotal (95% CI)	**1678**	**1680**		**60.8 %**	**0.91 [0.76, 1.08]**
Total events: 308 (LABA/LAMA), 334 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.12 (P = 0.26)					
2 Low-risk					
Donohue 2015a	6/353	10/353		3.0 %	0.59 [0.21, 1.65]
Donohue 2015b	11/349	13/348		4.7 %	0.84 [0.37, 1.90]
Hoshino 2015	0/22	0/21			Not estimable
Singh 2015c	7/358	2/358		1.3 %	3.55 [0.73, 17.21]
Vogelmeier 2013a	13/258	14/264		5.2 %	0.95 [0.44, 2.06]
Vogelmeier 2016	35/467	33/466		12.1 %	1.06 [0.65, 1.74]
Vogelmeier 2017	22/811	6/269		3.8 %	1.22 [0.49, 3.05]
Zhong 2015	20/372	35/369		9.3 %	0.54 [0.31, 0.96]
Subtotal (95% CI)	**2990**	**2448**		**39.2 %**	**0.88 [0.64, 1.22]**
Total events: 114 (LABA/LAMA), 113 (LABA/ICS)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 7.46, df = 6 (P = 0.28); I^2 =20%					
Test for overall effect: Z = 0.76 (P = 0.45)					
Total (95% CI)	**4668**	**4128**		**100.0 %**	**0.89 [0.75, 1.07]**
Total events: 422 (LABA/LAMA), 447 (LABA/ICS)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 7.50, df = 7 (P = 0.38); I^2 =7%					
Test for overall effect: Z = 1.23 (P = 0.22)					
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.89), I^2 =0.0%					



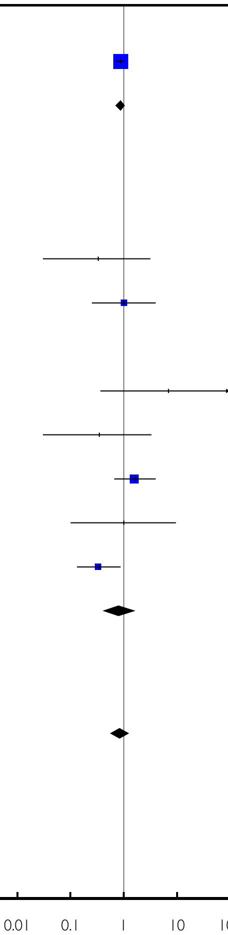
Analysis 1.16. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 16 COPD SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 16 COPD SAE

Study or subgroup	LABA/LAMA n/N	LABA/ICS n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2016	182/1678	207/1680		49.4 %	0.87 [0.70, 1.07]
Subtotal (95% CI)	**1678**	**1680**		**49.4 %**	**0.87 [0.70, 1.07]**
Total events: 182 (LABA/LAMA), 207 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.33 (P = 0.18)					
2 Low-risk					
Donohue 2015a	1/353	3/353		3.3 %	0.33 [0.03, 3.20]
Donohue 2015b	4/349	4/348		7.9 %	1.00 [0.25, 4.02]
Hoshino 2015	0/22	0/21			Not estimable
Singh 2015c	3/358	0/358		2.0 %	7.06 [0.36, 137.16]
Vogelmeier 2013a	1/258	3/264		3.3 %	0.34 [0.03, 3.28]
Vogelmeier 2016	13/467	8/466		16.1 %	1.64 [0.67, 3.99]
Vogelmeier 2017	3/811	1/269		3.3 %	1.00 [0.10, 9.61]
Zhong 2015	6/372	17/369		14.8 %	0.34 [0.13, 0.87]
Subtotal (95% CI)	**2990**	**2448**		**50.6 %**	**0.80 [0.39, 1.64]**
Total events: 31 (LABA/LAMA), 36 (LABA/ICS)					
Heterogeneity: Tau^2 = 0.29; Chi^2 = 9.01, df = 6 (P = 0.17); I^2 =33%					
Test for overall effect: Z = 0.61 (P = 0.54)					
Total (95% CI)	**4668**	**4128**		**100.0 %**	**0.83 [0.54, 1.27]**
Total events: 213 (LABA/LAMA), 243 (LABA/ICS)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 9.08, df = 7 (P = 0.25); I^2 =23%					
Test for overall effect: Z = 0.86 (P = 0.39)					
Test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.83), I^2 =0.0%					



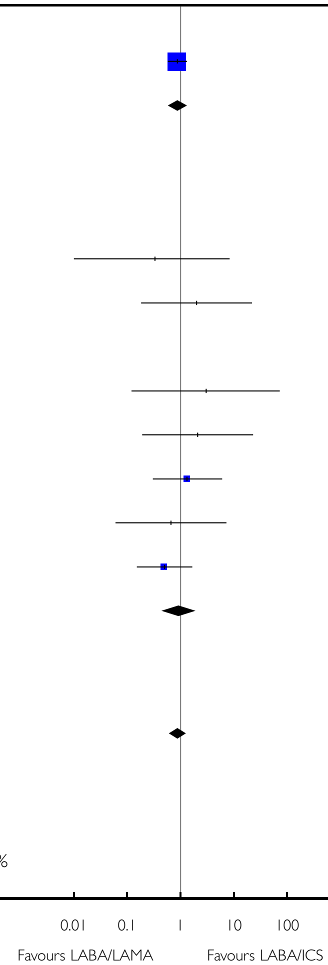
Analysis 1.17. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 17 Cardiac SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 17 Cardiac SAE

Study or subgroup	LABA/LAMA n/N	LABA/ICS n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2016	45/1678	52/1680		76.8 %	0.86 [0.58, 1.29]
Subtotal (95% CI)	**1678**	**1680**		**76.8 %**	**0.86 [0.58, 1.29]**
Total events: 45 (LABA/LAMA), 52 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.47)					
2 Low-risk					
Donohue 2015a	0/353	1/353		1.2 %	0.33 [0.01, 8.19]
Donohue 2015b	2/349	1/348		2.2 %	2.00 [0.18, 22.16]
Hoshino 2015	0/22	0/21			Not estimable
Singh 2015c	1/358	0/358		1.2 %	3.01 [0.12, 74.10]
Vogelmeier 2013a	2/258	1/264		2.2 %	2.05 [0.19, 22.80]
Vogelmeier 2016	4/467	3/466		5.6 %	1.33 [0.30, 5.99]
Vogelmeier 2017	2/811	1/269		2.2 %	0.66 [0.06, 7.34]
Zhong 2015	4/372	8/369		8.6 %	0.49 [0.15, 1.64]
Subtotal (95% CI)	**2990**	**2448**		**23.2 %**	**0.90 [0.43, 1.89]**
Total events: 15 (LABA/LAMA), 15 (LABA/ICS)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.09$, df = 6 (P = 0.80); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.27 (P = 0.79)					
Total (95% CI)	**4668**	**4128**		**100.0 %**	**0.87 [0.61, 1.24]**
Total events: 60 (LABA/LAMA), 67 (LABA/ICS)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.10$, df = 7 (P = 0.88); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.76 (P = 0.45)					
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.91), $I^2 = 0.0\%$					



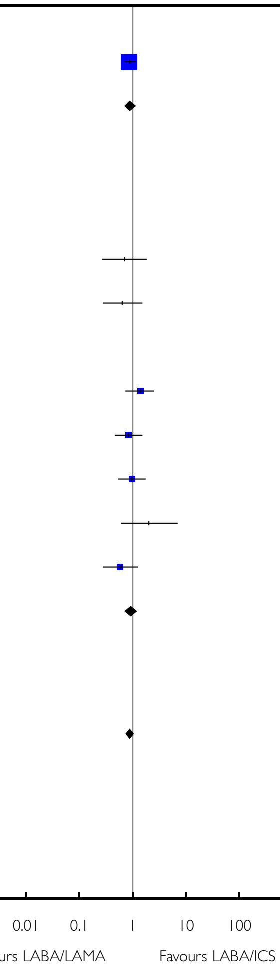
Analysis 1.18. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 18 Dropouts due to adverse events.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 18 Dropouts due to adverse events

Study or subgroup	LABA/LAMA n/N	LABA/ICS n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2016	129/1678	145/1680		55.7 %	0.88 [0.69, 1.13]
Subtotal (95% CI)	**1678**	**1680**		**55.7 %**	**0.88 [0.69, 1.13]**
Total events: 129 (LABA/LAMA), 145 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.00 (P = 0.32)					
2 Low-risk					
Donohue 2015a	7/353	10/353		3.6 %	0.69 [0.26, 1.84]
Donohue 2015b	9/349	14/348		4.7 %	0.63 [0.27, 1.48]
Hoshino 2015	0/22	0/21			Not estimable
Singh 2015c	24/358	18/358		8.6 %	1.36 [0.72, 2.55]
Vogelmeier 2013a	22/258	27/264		9.8 %	0.82 [0.45, 1.48]
Vogelmeier 2016	22/467	23/466		9.5 %	0.95 [0.52, 1.73]
Vogelmeier 2017	18/811	3/269		2.3 %	2.01 [0.59, 6.89]
Zhong 2015	11/372	18/369		5.8 %	0.59 [0.28, 1.28]
Subtotal (95% CI)	**2990**	**2448**		**44.3 %**	**0.90 [0.68, 1.19]**
Total events: 113 (LABA/LAMA), 113 (LABA/ICS)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.49$, df = 6 (P = 0.48); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.75 (P = 0.45)					
Total (95% CI)	**4668**	**4128**		**100.0 %**	**0.89 [0.74, 1.07]**
Total events: 242 (LABA/LAMA), 258 (LABA/ICS)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.50$, df = 7 (P = 0.60); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.25 (P = 0.21)					
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.92), $I^2 = 0.0\%$					



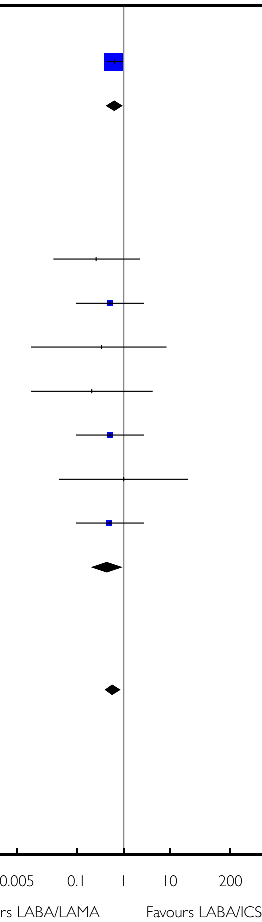
Analysis 1.19. Comparison 1 LABA/LAMA vs LABA/ICS, Outcome 19 Pneumonia.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 1 LABA/LAMA vs LABA/ICS

Outcome: 19 Pneumonia

Study or subgroup	LABA/LAMA n/N	LABA/ICS n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2016	34/1678	54/1680		77.4 %	0.62 [0.40, 0.96]
Subtotal (95% CI)	**1678**	**1680**		**77.4 %**	**0.62 [0.40, 0.96]**
Total events: 34 (LABA/LAMA), 54 (LABA/ICS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.14 (P = 0.033)					
2 Low-risk					
Donohue 2015a	1/353	4/353		3.0 %	0.25 [0.03, 2.23]
Donohue 2015b	2/349	4/348		5.0 %	0.50 [0.09, 2.72]
Singh 2015c	0/358	1/358		1.4 %	0.33 [0.01, 8.19]
Vogelmeier 2013a	0/258	2/264		1.6 %	0.20 [0.01, 4.25]
Vogelmeier 2016	2/467	4/466		5.0 %	0.50 [0.09, 2.73]
Vogelmeier 2017	1/811	0/269		1.4 %	1.00 [0.04, 24.56]
Zhong 2015	2/372	4/369		5.0 %	0.49 [0.09, 2.71]
Subtotal (95% CI)	**2968**	**2427**		**22.6 %**	**0.43 [0.19, 0.97]**
Total events: 8 (LABA/LAMA), 19 (LABA/ICS)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.85$, df = 6 (P = 0.99); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.04 (P = 0.041)					
Total (95% CI)	**4646**	**4107**		**100.0 %**	**0.57 [0.39, 0.84]**
Total events: 42 (LABA/LAMA), 73 (LABA/ICS)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.46$, df = 7 (P = 0.98); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.85 (P = 0.0044)					
Test for subgroup differences: $Chi^2 = 0.61$, df = 1 (P = 0.43), $I^2 = 0.0\%$					



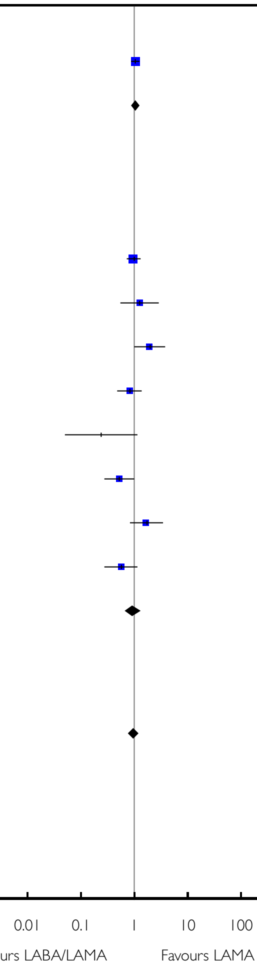
Analysis 2.1. Comparison 2 LABA/LAMA vs LAMA, Outcome 1 Moderate to severe exacerbations.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 1 Moderate to severe exacerbations

Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2013	419/729	828/1477		23.6 %	1.06 [0.89, 1.27]
Subtotal (95% CI)	**729**	**1477**		**23.6 %**	**1.06 [0.89, 1.27]**
Total events: 419 (LABA/LAMA), 828 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					
2 Low-risk					
Bateman 2013	85/474	174/953		19.8 %	0.98 [0.73, 1.30]
Decramer 2014a	14/212	11/208		6.9 %	1.27 [0.56, 2.86]
Decramer 2014b	26/217	14/215		8.9 %	1.95 [0.99, 3.85]
Donohue 2013	27/413	33/418		12.1 %	0.82 [0.48, 1.38]
Kerwin 2017	2/247	8/247		2.3 %	0.24 [0.05, 1.16]
Maleki-Yazdi 2014	16/454	29/451		9.9 %	0.53 [0.28, 0.99]
Tashkin 2009	21/124	14/131		8.1 %	1.70 [0.82, 3.52]
Vogelmeier 2008	13/207	23/221		8.4 %	0.58 [0.28, 1.17]
Subtotal (95% CI)	**2348**	**2844**		**76.4 %**	**0.93 [0.66, 1.30]**
Total events: 204 (LABA/LAMA), 306 (LAMA)					
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 15.80$, df = 7 (P = 0.03); I^2 =56%					
Test for overall effect: Z = 0.43 (P = 0.67)					
Total (95% CI)	**3077**	**4321**		**100.0 %**	**0.96 [0.75, 1.23]**
Total events: 623 (LABA/LAMA), 1134 (LAMA)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 16.51$, df = 8 (P = 0.04); I^2 =52%					
Test for overall effect: Z = 0.30 (P = 0.77)					
Test for subgroup differences: $Chi^2 = 0.45$, df = 1 (P = 0.50), I^2 =0.0%					



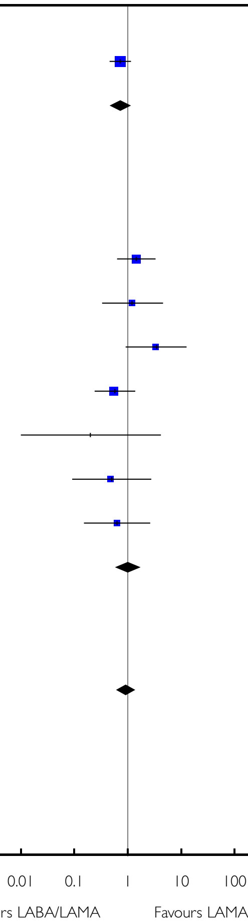
Analysis 2.2. Comparison 2 LABA/LAMA vs LAMA, Outcome 2 Severe exacerbations.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 2 Severe exacerbations

Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Aaron 2007	48/148	62/156		34.0 %	0.73 [0.45, 1.16]
Subtotal (95% CI)	**148**	**156**		**34.0 %**	**0.73 [0.45, 1.16]**
Total events: 48 (LABA/LAMA), 62 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.32 (P = 0.19)					
2 Low-risk					
Bateman 2013	10/474	14/953		18.0 %	1.45 [0.64, 3.28]
Decramer 2014a	5/212	4/208		8.4 %	1.23 [0.33, 4.65]
Decramer 2014b	10/217	3/215		8.7 %	3.41 [0.93, 12.58]
Donohue 2013	8/413	14/418		16.3 %	0.57 [0.24, 1.37]
Kerwin 2017	0/247	2/247		1.8 %	0.20 [0.01, 4.15]
Maleki-Yazdi 2014	2/454	4/451		5.4 %	0.49 [0.09, 2.71]
Vogelmeier 2008	3/207	5/221		7.3 %	0.64 [0.15, 2.69]
Subtotal (95% CI)	**2224**	**2713**		**66.0 %**	**0.99 [0.57, 1.72]**
Total events: 38 (LABA/LAMA), 46 (LAMA)					
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 7.97$, df = 6 (P = 0.24); $I^2 = 25\%$					
Test for overall effect: Z = 0.03 (P = 0.98)					
Total (95% CI)	**2372**	**2869**		**100.0 %**	**0.90 [0.59, 1.36]**
Total events: 86 (LABA/LAMA), 108 (LAMA)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 8.91$, df = 7 (P = 0.26); $I^2 = 21\%$					
Test for overall effect: Z = 0.52 (P = 0.61)					
Test for subgroup differences: $Chi^2 = 0.70$, df = 1 (P = 0.40), $I^2 = 0.0\%$					



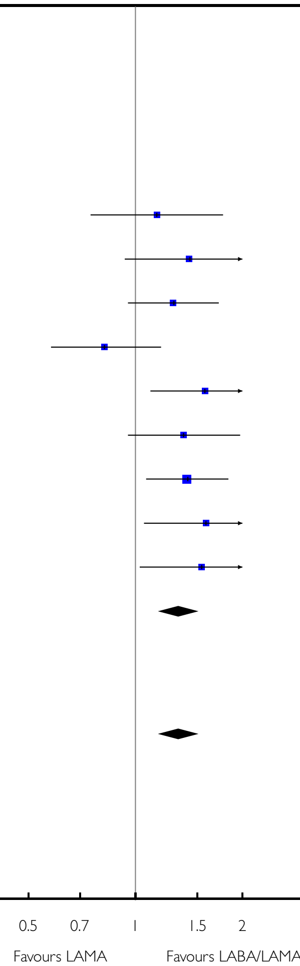
Analysis 2.3. Comparison 2 LABA/LAMA vs LAMA, Outcome 3 SGRQ responders at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 3 SGRQ responders at 3 months

Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low-risk					
Decramer 2014a	106/178	95/169		8.2 %	1.15 [0.75, 1.76]
Decramer 2014b	111/174	99/179		8.2 %	1.42 [0.93, 2.18]
Donohue 2013	216/359	188/347		14.8 %	1.28 [0.95, 1.72]
Kerwin 2017	104/242	117/245		11.1 %	0.82 [0.58, 1.18]
Mahler 2015a	141/246	112/243		11.1 %	1.57 [1.10, 2.24]
Mahler 2015b	141/238	122/237		10.8 %	1.37 [0.95, 1.97]
Maleki-Yazdi 2014	244/437	199/419		17.3 %	1.40 [1.07, 1.83]
Singh 2015a	104/196	80/192		9.2 %	1.58 [1.06, 2.36]
Singh 2015b	102/197	79/192		9.2 %	1.54 [1.03, 2.29]
Subtotal (95% CI)	**2267**	**2223**		**100.0 %**	**1.32 [1.16, 1.51]**
Total events: 1269 (LABA/LAMA), 1091 (LAMA)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 9.71, df = 8 (P = 0.29); I^2 =18%					
Test for overall effect: Z = 4.16 (P = 0.000031)					
Total (95% CI)	**2267**	**2223**		**100.0 %**	**1.32 [1.16, 1.51]**
Total events: 1269 (LABA/LAMA), 1091 (LAMA)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 9.71, df = 8 (P = 0.29); I^2 =18%					
Test for overall effect: Z = 4.16 (P = 0.000031)					
Test for subgroup differences: Not applicable					



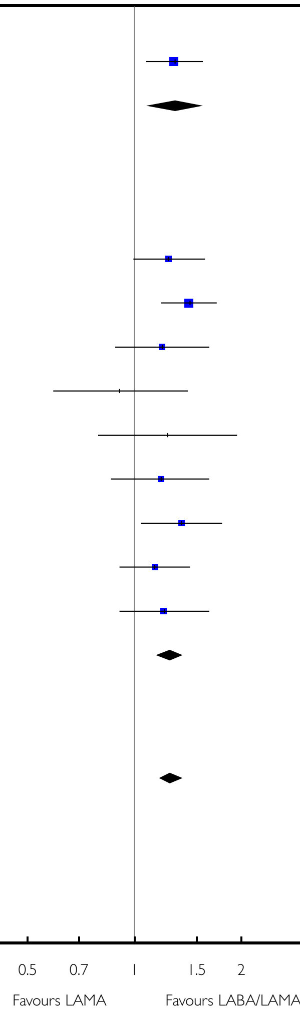
Analysis 2.4. Comparison 2 LABA/LAMA vs LAMA, Outcome 4 SGRQ responders at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 4 SGRQ responders at 6 months

Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2013	408/684	711/1335		18.7 %	1.30 [1.08, 1.56]
Subtotal (95% CI)	**684**	**1335**		**18.7 %**	**1.30 [1.08, 1.56]**
Total events: 408 (LABA/LAMA), 711 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.73 (P = 0.0063)					
2 Low-risk					
Bateman 2013	281/441	514/880		11.7 %	1.25 [0.99, 1.58]
Buhl 2015a%b	563/979	465/955		20.3 %	1.43 [1.19, 1.71]
D'Urzo 2017	194/335	180/337		7.0 %	1.20 [0.88, 1.63]
Decramer 2014a	94/168	92/158		3.4 %	0.91 [0.59, 1.41]
Decramer 2014b	103/155	104/169		3.1 %	1.24 [0.79, 1.95]
Donohue 2013	188/317	172/312		6.5 %	1.19 [0.86, 1.63]
Maleki-Yazdi 2014	237/445	196/430		9.2 %	1.36 [1.04, 1.77]
Martinez 2017a	187/503	294/860		12.4 %	1.14 [0.91, 1.43]
Martinez 2017b	169/430	126/362		7.7 %	1.21 [0.91, 1.62]
Subtotal (95% CI)	**3773**	**4463**		**81.3 %**	**1.26 [1.15, 1.37]**
Total events: 2016 (LABA/LAMA), 2143 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.29$, df = 8 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 4.98 (P < 0.00001)					
Total (95% CI)	**4457**	**5798**		**100.0 %**	**1.26 [1.17, 1.37]**
Total events: 2424 (LABA/LAMA), 2854 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.39$, df = 9 (P = 0.80); I^2 =0.0%					
Test for overall effect: Z = 5.67 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.10$, df = 1 (P = 0.76), I^2 =0.0%					



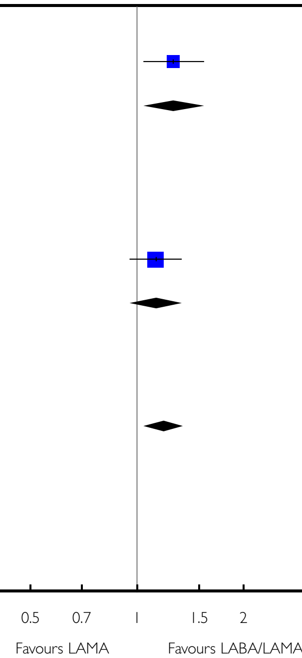
Analysis 2.5. Comparison 2 LABA/LAMA vs LAMA, Outcome 5 SGRQ responders at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 5 SGRQ responders at 12 months

Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2013	341/600	582/1143		42.0 %	1.27 [1.04, 1.55]
Subtotal (95% CI)	**600**	**1143**		**42.0 %**	**1.27 [1.04, 1.55]**
Total events: 341 (LABA/LAMA), 582 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.35 (P = 0.019)					
2 Low-risk					
Hanania 2003	411/995	490/1277		58.0 %	1.13 [0.95, 1.34]
Subtotal (95% CI)	**995**	**1277**		**58.0 %**	**1.13 [0.95, 1.34]**
Total events: 411 (LABA/LAMA), 490 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.42 (P = 0.16)					
Total (95% CI)	**1595**	**2420**		**100.0 %**	**1.19 [1.04, 1.35]**
Total events: 752 (LABA/LAMA), 1072 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.76$, df = 1 (P = 0.38); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.60 (P = 0.0092)					
Test for subgroup differences: $Chi^2 = 0.76$, df = 1 (P = 0.38), $I^2 = 0.0\%$					



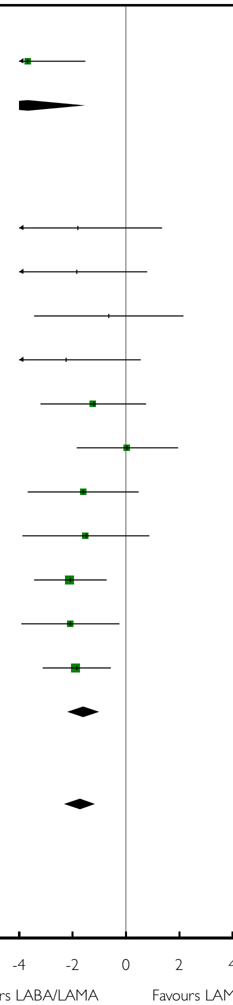
Analysis 2.6. Comparison 2 LABA/LAMA vs LAMA, Outcome 6 Change from baseline in SGRQ at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 6 Change from baseline in SGRQ at 3 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2013	694	-8.31 (23.84)	1370	-4.63 (23.18)		6.9 %	-3.68 [-5.84, -1.52]
Subtotal (95% CI)	**694**		**1370**			**6.9 %**	**-3.68 [-5.84, -1.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.34 (P = 0.00083)							
2 Low-risk							
Asai 2013	119	-4.5 (10.91)	39	-2.7 (7.84)		3.3 %	-1.80 [-4.95, 1.35]
Bateman 2013	474	-9.4 (24.1)	953	-7.56 (23.74)		4.6 %	-1.84 [-4.48, 0.80]
Decramer 2014a	178	-7.48 (13.29)	169	-6.84 (13.241)		4.1 %	-0.64 [-3.43, 2.15]
Decramer 2014b	174	-9.79 (14.274)	179	-7.53 (12.609)		4.1 %	-2.26 [-5.07, 0.55]
Donohue 2013	359	-8.17 (13.04)	347	-6.95 (13.62)		8.3 %	-1.22 [-3.19, 0.75]
Kerwin 2017	247	-4.07 (10.62)	247	-4.12 (10.88)		9.0 %	0.05 [-1.85, 1.95]
Mahler 2015a	246	-6.4 (11.8)	243	-4.8 (11.7)		7.4 %	-1.60 [-3.68, 0.48]
Mahler 2015b	238	-7.5 (13.1)	237	-6 (13.2)		5.8 %	-1.50 [-3.87, 0.87]
Maleki-Yazdi 2014	445	-7.02 (10.27)	430	-4.93 (10.31)		17.4 %	-2.09 [-3.45, -0.73]
Singh 2015a%b	393	-4.97 (13)	384	-2.88 (13.1)		9.6 %	-2.09 [-3.93, -0.25]
ZuWallack 2014a%b	1039	-5.982 (14.99)	1055	-4.13 (15.14)		19.4 %	-1.85 [-3.14, -0.56]
Subtotal (95% CI)	**3912**		**4283**			**93.1 %**	**-1.60 [-2.19, -1.01]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.69, df = 10 (P = 0.91); I^2 =0.0%							
Test for overall effect: Z = 5.32 (P < 0.00001)							
Total (95% CI)	**4606**		**5653**			**100.0 %**	**-1.74 [-2.31, -1.18]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 8.01, df = 11 (P = 0.71); I^2 =0.0%							
Test for overall effect: Z = 6.02 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 3.32, df = 1 (P = 0.07), I^2 =70%							



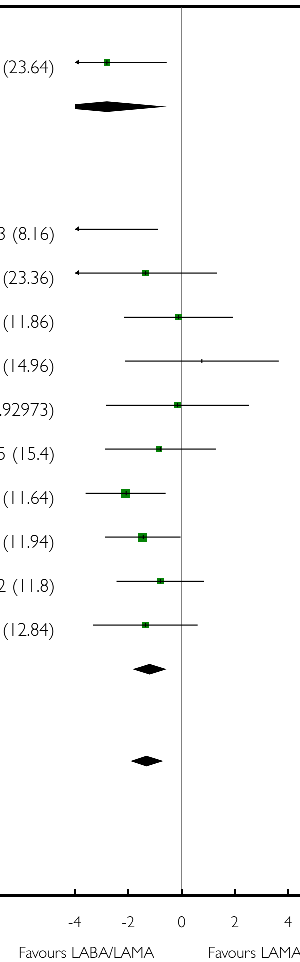
Analysis 2.7. Comparison 2 LABA/LAMA vs LAMA, Outcome 7 Change from baseline in SGRQ at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 7 Change from baseline in SGRQ at 6 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2013	684	-8.94 (24.45)	1335	-6.15 (23.64)		7.5 %	-2.79 [-5.02, -0.56]
Subtotal (95% CI)	**684**		**1335**			**7.5 %**	**-2.79 [-5.02, -0.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.45 (P = 0.014)							
2 Low-risk							
Asai 2013	119	-4.5 (11.7)	39	-0.3 (8.16)		3.4 %	-4.20 [-7.51, -0.89]
Bateman 2013	441	-9.82 (23.7)	880	-8.45 (23.36)		5.1 %	-1.37 [-4.07, 1.33]
D'Urzo 2014	256	-6.57 (11.84)	257	-6.44 (11.86)		8.8 %	-0.13 [-2.18, 1.92]
Decramer 2014a	207	-6.87 (14.68)	203	-7.62 (14.96)		4.5 %	0.75 [-2.12, 3.62]
Decramer 2014b	217	-9.95 (14.4363)	215	-9.78 (13.92973)		5.2 %	-0.17 [-2.85, 2.51]
Donohue 2013	413	-8.07 (15.22)	418	-7.25 (15.4)		8.5 %	-0.82 [-2.90, 1.26]
Maleki-Yazdi 2014	454	-7.27 (11.46)	451	-5.17 (11.64)		16.0 %	-2.10 [-3.61, -0.59]
Martinez 2017a	432	-3.3 (12.06)	739	-1.84 (11.94)		17.7 %	-1.46 [-2.89, -0.03]
Martinez 2017b	430	-3 (11.82)	362	-2.2 (11.8)		13.4 %	-0.80 [-2.45, 0.85]
Singh 2014	338	-7.16 (12.8693)	327	-5.8 (12.84)		9.7 %	-1.36 [-3.31, 0.59]
Subtotal (95% CI)	**3307**		**3891**			**92.5 %**	**-1.20 [-1.83, -0.57]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.43$, df = 9 (P = 0.49); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.73 (P = 0.00019)							
Total (95% CI)	**3991**		**5226**			**100.0 %**	**-1.31 [-1.93, -0.70]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.25$, df = 10 (P = 0.42); $I^2 = 2\%$							
Test for overall effect: Z = 4.18 (P = 0.000029)							
Test for subgroup differences: $Chi^2 = 1.82$, df = 1 (P = 0.18), $I^2 = 45\%$							



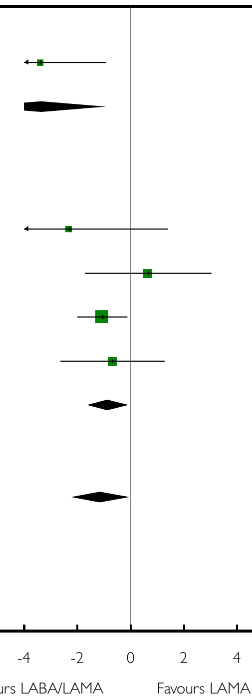
Analysis 2.8. Comparison 2 LABA/LAMA vs LAMA, Outcome 8 Change from baseline in SGRQ at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 8 Change from baseline in SGRQ at 12 months

Study or subgroup	LABA/LAMA N	LABA/LAMA Mean(SD)	LAMA N	LAMA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2013	729	-9.61 (27.68)	1477	-6.23 (27.48)		14.8 %	-3.38 [-5.83, -0.93]
Subtotal (95% CI)	**729**		**1477**			**14.8 %**	**-3.38 [-5.83, -0.93]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.70 (P = 0.0068)							
2 Low-risk							
Asai 2013	119	-2.9 (10.99)	39	-0.6 (9.92)		7.6 %	-2.30 [-5.99, 1.39]
D'Urzo 2017	335	-3.646 (15.76)	337	-4.31 (15.55)		15.6 %	0.66 [-1.71, 3.03]
Hanania 2017	995	-3.3 (11.27)	1277	-2.24 (11.051)		41.7 %	-1.06 [-1.99, -0.13]
RADIATE 2016	343	-6.79 (12.611)	349	-6.12 (13.695)		20.3 %	-0.67 [-2.63, 1.29]
Subtotal (95% CI)	**1792**		**2002**			**85.2 %**	**-0.87 [-1.64, -0.10]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.38$, df = 3 (P = 0.50); I^2 =0.0%							
Test for overall effect: Z = 2.21 (P = 0.027)							
Total (95% CI)	**2521**		**3479**			**100.0 %**	**-1.15 [-2.24, -0.06]**
Heterogeneity: $Tau^2 = 0.52$; $Chi^2 = 6.05$, df = 4 (P = 0.20); I^2 =34%							
Test for overall effect: Z = 2.07 (P = 0.038)							
Test for subgroup differences: $Chi^2 = 3.67$, df = 1 (P = 0.06), I^2 =73%							



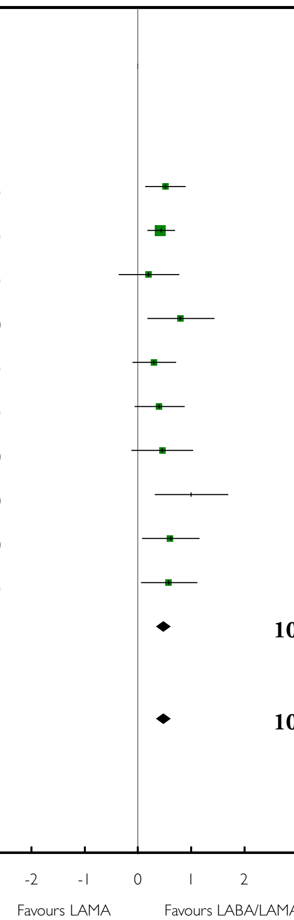
Analysis 2.9. Comparison 2 LABA/LAMA vs LAMA, Outcome 9 TDI at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 9 TDI at 3 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Bateman 2013	474	2.44 (3.44)	953	1.92 (3.45)		14.2 %	0.52 [0.14, 0.90]
Buhl 2015a%b	992	2.136 (3.024)	978	1.7 (3.033)		28.5 %	0.43 [0.17, 0.70]
Decramer 2014a	179	2.2 (2.68)	184	2 (2.85)		6.3 %	0.20 [-0.37, 0.77]
Decramer 2014b	161	2.6 (2.9)	172	1.8 (3)		5.1 %	0.80 [0.17, 1.43]
Donohue 2013	372	2.3 (2.85)	359	2 (2.85)		12.0 %	0.30 [-0.11, 0.71]
Kerwin 2017	233	2.3 (2.58)	235	1.9 (2.64)		9.1 %	0.40 [-0.07, 0.87]
Mahler 2015a	246	1.94 (3.3)	246	1.48 (3.3)		6.0 %	0.46 [-0.12, 1.04]
Mahler 2015b	233	2.88 (3.8)	232	1.88 (3.8)		4.3 %	1.00 [0.31, 1.69]
Singh 2015a	196	1.939 (2.7)	193	1.33 (2.7)		7.1 %	0.61 [0.07, 1.15]
Singh 2015b	197	1.531 (2.625)	192	0.95 (2.65)		7.4 %	0.58 [0.06, 1.11]
Subtotal (95% CI)	**3283**		**3744**			**100.0 %**	**0.48 [0.34, 0.62]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.45$, df = 9 (P = 0.79); I^2 =0.0%							
Test for overall effect: Z = 6.58 (P < 0.00001)							
Total (95% CI)	**3283**		**3744**			**100.0 %**	**0.48 [0.34, 0.62]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.45$, df = 9 (P = 0.79); I^2 =0.0%							
Test for overall effect: Z = 6.58 (P < 0.00001)							
Test for subgroup differences: Not applicable							



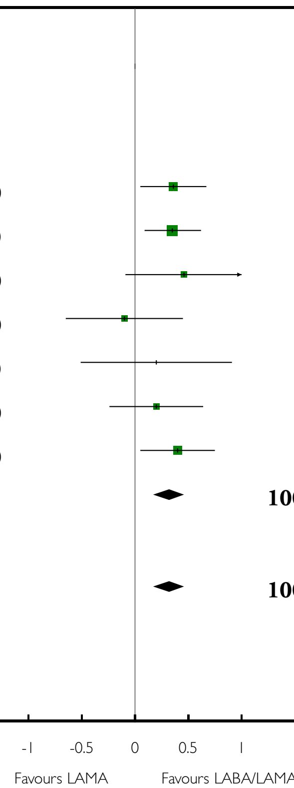
Analysis 2.10. Comparison 2 LABA/LAMA vs LAMA, Outcome 10 TDI at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 10 TDI at 6 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Bateman 2013	474	2.72 (2.83)	953	2.36 (2.79)		22.4 %	0.36 [0.05, 0.67]
Buhl 2015a%b	992	1.98 (2.99)	978	1.63 (3.002)		30.9 %	0.35 [0.09, 0.62]
D'Urzo 2014	260	2.02 (3.2249)	263	1.56 (3.24)		7.0 %	0.46 [-0.09, 1.01]
Decramer 2014a	207	2.3 (2.88)	203	2.4 (2.85)		7.0 %	-0.10 [-0.65, 0.45]
Decramer 2014b	217	2.3 (4.419276)	215	2.1 (2.932576)		4.3 %	0.20 [-0.51, 0.91]
Donohue 2013	336	2.4 (2.93)	326	2.2 (2.89)		11.0 %	0.20 [-0.24, 0.64]
Singh 2014	344	2.51 (1.11283)	331	2.11 (3.09)		17.3 %	0.40 [0.05, 0.75]
Subtotal (95% CI)	**2830**		**3269**			**100.0 %**	**0.32 [0.17, 0.46]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.16$, df = 6 (P = 0.79); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.20 (P = 0.000027)							
Total (95% CI)	**2830**		**3269**			**100.0 %**	**0.32 [0.17, 0.46]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.16$, df = 6 (P = 0.79); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.20 (P = 0.000027)							
Test for subgroup differences: Not applicable							



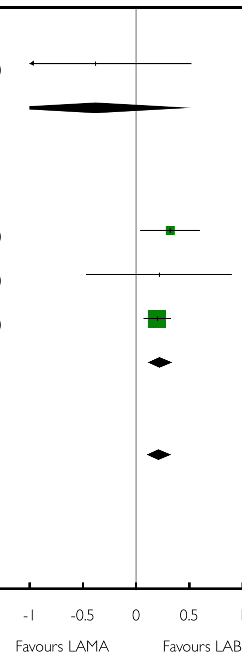
Analysis 2.11. Comparison 2 LABA/LAMA vs LAMA, Outcome 11 TDI at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 11 TDI at 12 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Aaron 2007	148	1.4 (3.96)	156	1.78 (4.08)		1.6 %	-0.38 [-1.28, 0.52]
Subtotal (95% CI)	**148**		**156**			**1.6 %**	**-0.38 [-1.28, 0.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.82 (P = 0.41)							
2 Low-risk							
Buhl 2015a%b	992	2.058 (3.118)	978	1.74 (3.159)		17.3 %	0.32 [0.04, 0.60]
D'Urzo 2017	335	1.812 (4.59)	337	1.6 (4.42)		2.9 %	0.22 [-0.47, 0.90]
Hanania 2017	1002	0.5 (1.62)	1309	0.3 (1.54)		78.2 %	0.20 [0.07, 0.33]
Subtotal (95% CI)	**2329**		**2624**			**98.4 %**	**0.22 [0.11, 0.34]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.61$, df = 2 (P = 0.74); I^2 =0.0%							
Test for overall effect: Z = 3.74 (P = 0.00018)							
Total (95% CI)	**2477**		**2780**			**100.0 %**	**0.21 [0.10, 0.33]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.29$, df = 3 (P = 0.52); I^2 =0.0%							
Test for overall effect: Z = 3.60 (P = 0.00031)							
Test for subgroup differences: $Chi^2 = 1.68$, df = 1 (P = 0.20), I^2 =40%							



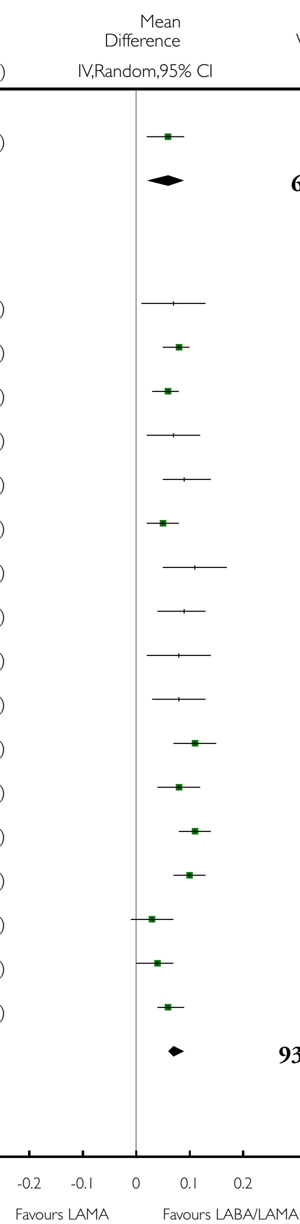
Analysis 2.12. Comparison 2 LABA/LAMA vs LAMA, Outcome 12 Change from baseline in FEV1 at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 12 Change from baseline in FEV1 at 3 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LAMA N	Mean(SD)	Weight	Mean Difference IV,Random,95% CI
1 High-risk						
Wedzicha 2013	666	0.17 (0.387)	1316	0.12 (0.328)	6.2 %	0.06 [0.02, 0.09]
Subtotal (95% CI)	**666**		**1316**		**6.2 %**	**0.06 [0.02, 0.09]**
Heterogeneity: not applicable						
Test for overall effect: Z = 3.14 (P = 0.0017)						
2 Low-risk						
Asai 2013	113	0.209 (0.173)	38	0.14 (0.156)	2.8 %	0.07 [0.01, 0.13]
Buhl 2015a	521	0.146 (0.205)	520	0.07 (0.205)	8.8 %	0.08 [0.05, 0.10]
Buhl 2015b	497	0.147 (0.201)	498	0.09 (0.201)	8.7 %	0.06 [0.03, 0.08]
Decramer 2014a	193	0.18 (0.248)	181	0.11 (0.255)	3.6 %	0.07 [0.02, 0.12]
Decramer 2014b	181	0.203 (0.2064)	188	0.11 (0.2347)	4.3 %	0.09 [0.05, 0.14]
Donohue 2013	371	0.182 (0.218)	358	0.13 (0.244)	6.4 %	0.05 [0.02, 0.08]
Hoshino 2014	18	0.165 (0.013)	16	0.06 (0.119)	2.9 %	0.11 [0.05, 0.17]
Kerwin 2017	247	0.064 (0.242)	247	-0.02 (0.2389)	4.7 %	0.09 [0.04, 0.13]
Mahler 2012a	561	0.23 (0.497)	549	0.15 (0.492)	2.9 %	0.08 [0.02, 0.14]
Mahler 2012b	565	0.2 (0.428)	564	0.12 (0.427)	3.7 %	0.08 [0.03, 0.13]
Mahler 2015a	256	0.201 (0.23)	260	0.09 (0.229)	5.2 %	0.11 [0.07, 0.15]
Mahler 2015b	246	0.208 (0.223)	249	0.13 (0.224)	5.2 %	0.08 [0.04, 0.12]
Maleki-Yazdi 2014	423	0.19 (0.2417)	408	0.08 (0.2253)	6.8 %	0.11 [0.08, 0.14]
RADIATE 2016	373	0.1752 (0.20198)	373	0.08 (0.19606)	7.7 %	0.10 [0.07, 0.13]
Singh 2015a	200	0.163 (0.184)	200	0.14 (0.198)	5.6 %	0.03 [-0.01, 0.07]
Singh 2015b	199	0.163 (0.183)	197	0.12 (0.182)	5.9 %	0.04 [0.00, 0.07]
ZuWallack 2014a	548	0.195 (0.211)	551	0.13 (0.211)	8.7 %	0.06 [0.04, 0.09]
Subtotal (95% CI)	**5512**		**5397**		**93.8 %**	**0.07 [0.06, 0.09]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 25.85$, df = 16 (P = 0.06); I^2 =38%						
Test for overall effect: Z = 12.75 (P < 0.00001)						



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Study or subgroup	LABA/LAMA N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Total (95% CI)	**6178**		**6713**			**100.0 %**	**0.07 [0.06, 0.08]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 26.90$, df = 17 (P = 0.06); I^2 =37%							
Test for overall effect: Z = 13.10 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 1.11$, df = 1 (P = 0.29), I^2 =10%							

-0.2 -0.1 0 0.1 0.2

Favours LAMA Favours LABA/LAMA

Analysis 2.13. Comparison 2 LABA/LAMA vs LAMA, Outcome 13 Change from baseline in FEV1 at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 13 Change from baseline in FEV1 at 6 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2013	604	0.16 (0.371)	1176	0.1 (0.36)		7.0 %	0.06 [0.02, 0.10]
Subtotal (95% CI)	**604**		**1176**			**7.0 %**	**0.06 [0.02, 0.10]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.26 (P = 0.0011)							
2 Low-risk							
Asai 2013	113	0.198 (0.174)	37	0.12 (0.14)		4.1 %	0.08 [0.03, 0.14]
Bateman 2013	474	0.17 (0.544)	424	0.08 (0.494)		3.0 %	0.09 [0.02, 0.16]
Buhl 2015a	521	0.112 (0.205)	520	0.05 (0.205)		9.7 %	0.06 [0.04, 0.09]
Buhl 2015b	497	0.119 (0.201)	498	0.07 (0.201)		9.6 %	0.05 [0.03, 0.08]
D'Urzo 2014	271	0.095 (0.19754)	266	0.07 (0.196)		7.6 %	0.03 [0.00, 0.06]
Decramer 2014a	177	0.211 (0.243)	173	0.12 (0.245)		4.6 %	0.09 [0.04, 0.14]

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Favours LAMA Favours LABA/LAMA

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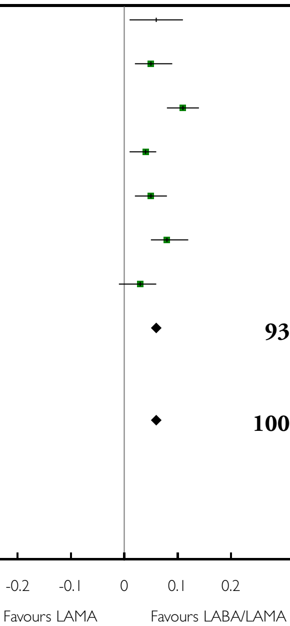
Study or subgroup	LABA/LAMA N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Decramer 2014b	161	0.208 (0.228394)	175	0.15 (0.238118)		4.8 %	0.06 [0.01, 0.11]
Donohue 2013	330	0.171 (0.229)	322	0.12 (0.226)		7.3 %	0.05 [0.02, 0.09]
Maleki-Yazdi 2014	454	0.205 (0.243)	451	0.09 (0.244)		8.0 %	0.11 [0.08, 0.14]
Martinez 2017a	429	0.126 (0.201)	734	0.09 (0.2)		9.9 %	0.04 [0.01, 0.06]
Martinez 2017b	433	0.116 (0.21)	367	0.06 (0.209)		8.6 %	0.05 [0.02, 0.08]
RADIATE 2016	356	0.1557 (0.21754)	358	0.07 (0.20358)		8.2 %	0.08 [0.05, 0.12]
Singh 2014	349	0.083 (0.22418)	332	0.06 (0.219)		7.6 %	0.03 [-0.01, 0.06]
Subtotal (95% CI)	**4565**		**4657**			**93.0 %**	**0.06 [0.05, 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 27.18, df = 12 (P = 0.01); I² =56%							
Test for overall effect: Z = 8.27 (P < 0.00001)							
Total (95% CI)	**5169**		**5833**			**100.0 %**	**0.06 [0.05, 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 27.19, df = 13 (P = 0.01); I² =52%							
Test for overall effect: Z = 8.88 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² =0.0%							



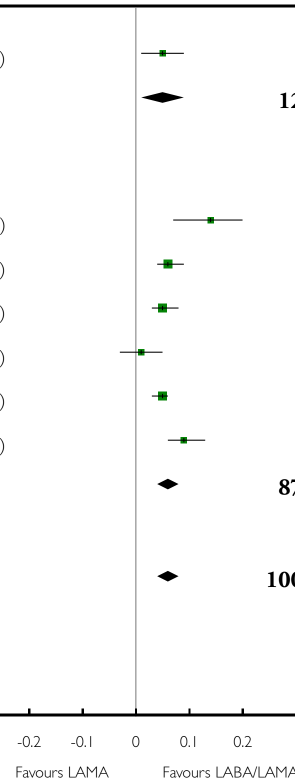
Analysis 2.14. Comparison 2 LABA/LAMA vs LAMA, Outcome 14 Change from baseline in FEV1 at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 14 Change from baseline in FEV1 at 12 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2013	729	0.14 (0.421)	1477	0.09 (0.427)		12.6 %	0.05 [0.01, 0.09]
Subtotal (95% CI)	**729**		**1477**			**12.6 %**	**0.05 [0.01, 0.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.61 (P = 0.0090)							
2 Low-risk							
Asai 2013	104	0.189 (0.173)	37	0.05 (0.17)		6.5 %	0.14 [0.07, 0.20]
Buhl 2015a	521	0.099 (0.205)	520	0.04 (0.205)		17.3 %	0.06 [0.04, 0.09]
Buhl 2015b	497	0.093 (0.201)	498	0.04 (0.201)		17.2 %	0.05 [0.03, 0.08]
D'Urzo 2017	335	0.038 (0.275)	337	0.03 (0.275)		11.3 %	0.01 [-0.03, 0.05]
Hanania 2017	1021	0.133 (0.179)	1317	0.09 (0.181)		21.4 %	0.05 [0.03, 0.06]
RADIATE 2016	333	0.1468 (0.22933)	346	0.06 (0.22433)		13.7 %	0.09 [0.06, 0.13]
Subtotal (95% CI)	**2811**		**3055**			**87.4 %**	**0.06 [0.04, 0.08]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 17.00, df = 5 (P = 0.005); I^2 =71%							
Test for overall effect: Z = 5.42 (P < 0.00001)							
Total (95% CI)	**3540**		**4532**			**100.0 %**	**0.06 [0.04, 0.08]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 17.05, df = 6 (P = 0.01); I^2 =65%							
Test for overall effect: Z = 6.03 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.22, df = 1 (P = 0.64), I^2 =0.0%							



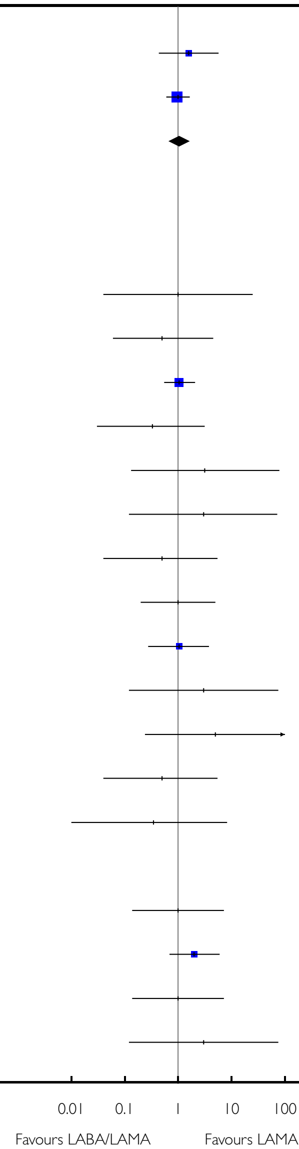
Analysis 2.15. Comparison 2 LABA/LAMA vs LAMA, Outcome 15 Mortality.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 15 Mortality

Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Aaron 2007	6/148	4/156		5.4 %	1.61 [0.44, 5.81]
Wedzicha 2013	23/729	47/1477		34.7 %	0.99 [0.60, 1.65]
Subtotal (95% CI)	**877**	**1633**		**40.1 %**	**1.06 [0.66, 1.69]**
Total events: 29 (LABA/LAMA), 51 (LAMA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.47, df = 1 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 0.23 (P = 0.82)					
2 Low-risk					
Asai 2013	1/119	0/39		0.9 %	1.00 [0.04, 25.05]
Bateman 2013	1/474	4/953		1.9 %	0.50 [0.06, 4.50]
Buhl 2015a%b	18/1029	17/1033		20.0 %	1.06 [0.55, 2.08]
D'Urzo 2014	1/335	3/337		1.7 %	0.33 [0.03, 3.22]
D'Urzo 2017	1/182	0/194		0.9 %	3.21 [0.13, 79.42]
Decramer 2014a	1/212	0/208		0.9 %	2.96 [0.12, 73.01]
Decramer 2014b	1/217	2/215		1.5 %	0.49 [0.04, 5.48]
Donohue 2013	3/413	3/418		3.5 %	1.01 [0.20, 5.04]
Hanania 2017	4/1036	5/1341		5.1 %	1.04 [0.28, 3.87]
Kerwin 2017	1/247	0/247		0.9 %	3.01 [0.12, 74.30]
Mahler 2012a	2/570	0/561		1.0 %	4.94 [0.24, 103.09]
Mahler 2012b	1/572	2/570		1.5 %	0.50 [0.04, 5.50]
Mahler 2015a	0/258	1/262		0.9 %	0.34 [0.01, 8.32]
Mahler 2015b	0/250	0/251			Not estimable
Maleki-Yazdi 2014	2/454	2/451		2.3 %	0.99 [0.14, 7.08]
RADIATE 2016	10/407	5/405		7.6 %	2.02 [0.68, 5.95]
Singh 2015a	2/203	2/203		2.3 %	1.00 [0.14, 7.17]
Singh 2015b	1/202	0/203		0.9 %	3.03 [0.12, 74.82]



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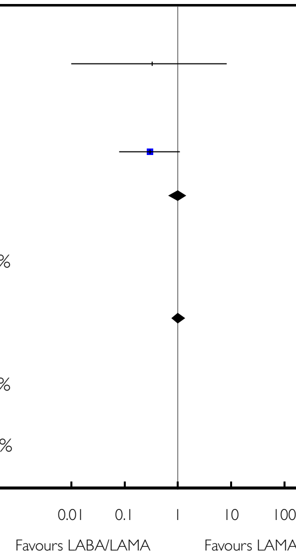
Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Tashkin 2009	0/124	0/131			Not estimable
Troosters 2016	0/76	1/76		0.9 %	0.33 [0.01, 8.20]
Vogelmeier 2008	0/207	0/221			Not estimable
ZuWallack 2014a%b	3/1133	10/1134		5.3 %	0.30 [0.08, 1.09]
Subtotal (95% CI)	**8720**	**9453**		**59.9 %**	**0.98 [0.66, 1.43]**
Total events: 53 (LABA/LAMA), 57 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 10.75$, df = 18 (P = 0.90); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.13 (P = 0.90)					
Total (95% CI)	**9597**	**11086**		**100.0 %**	**1.01 [0.75, 1.36]**
Total events: 82 (LABA/LAMA), 108 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 11.29$, df = 20 (P = 0.94); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.05 (P = 0.96)					
Test for subgroup differences: $Chi^2 = 0.07$, df = 1 (P = 0.79), $I^2 = 0.0\%$					



Analysis 2.16. Comparison 2 LABA/LAMA vs LAMA, Outcome 16 Total SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 16 Total SAE

Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Aaron 2007	9/148	10/156		1.2 %	0.95 [0.37, 2.40]
Wedzicha 2013	167/729	344/1477		22.5 %	0.98 [0.79, 1.21]
Subtotal (95% CI)	**877**	**1633**		**23.6 %**	**0.98 [0.80, 1.20]**
Total events: 176 (LABA/LAMA), 354 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.94); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.22 (P = 0.82)					
2 Low-risk					
Asai 2013	19/119	2/39		0.4 %	3.52 [0.78, 15.83]
Bateman 2013	22/474	48/953		3.7 %	0.92 [0.55, 1.54]
Buhl 2015a%b	169/1029	172/1033		18.5 %	0.98 [0.78, 1.24]
D'Urzo 2014	19/335	17/337		2.2 %	1.13 [0.58, 2.22]
D'Urzo 2017	14/182	15/194		1.7 %	0.99 [0.47, 2.12]
Decramer 2014a	7/212	13/208		1.1 %	0.51 [0.20, 1.31]
Decramer 2014b	22/217	9/215		1.6 %	2.58 [1.16, 5.75]
Donohue 2013	21/413	27/418		2.9 %	0.78 [0.43, 1.40]
Hanania 2017	114/1036	139/1341		14.5 %	1.07 [0.82, 1.39]
Kerwin 2017	7/247	6/247		0.8 %	1.17 [0.39, 3.54]
Mahler 2012a	21/570	17/561		2.4 %	1.22 [0.64, 2.35]
Mahler 2012b	19/572	18/570		2.3 %	1.05 [0.55, 2.03]
Mahler 2015a	10/258	8/262		1.1 %	1.28 [0.50, 3.30]
Mahler 2015b	6/250	12/251		1.0 %	0.49 [0.18, 1.33]
Maleki-Yazdi 2014	16/454	17/451		2.1 %	0.93 [0.47, 1.87]
RADIATE 2016	55/407	55/405		6.2 %	0.99 [0.67, 1.49]
Singh 2014	23/385	16/385		2.3 %	1.47 [0.76, 2.82]
Singh 2015a	4/203	6/203		0.6 %	0.66 [0.18, 2.37]

0.05 0.2 1 5 20

Favours LABA/LAMA Favours LAMA

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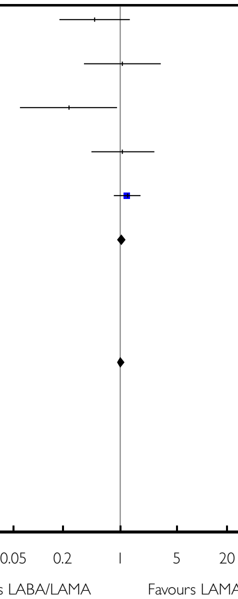
Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Singh 2015b	6/202	12/203		1.0 %	0.49 [0.18, 1.32]
Tashkin 2009	7/124	7/131		0.9 %	1.06 [0.36, 3.11]
Troosters 2016	3/76	11/76		0.6 %	0.24 [0.06, 0.91]
Vogelmeier 2008	10/207	10/221		1.2 %	1.07 [0.44, 2.63]
ZuWallack 2014a%b	64/1133	53/1134		7.1 %	1.22 [0.84, 1.77]
Subtotal (95% CI)	**9105**	**9838**		**76.4 %**	**1.03 [0.91, 1.16]**
Total events: 658 (LABA/LAMA), 690 (LAMA)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 23.07, df = 22 (P = 0.40); I^2 =5%					
Test for overall effect: Z = 0.40 (P = 0.69)					
Total (95% CI)	**9982**	**11471**		**100.0 %**	**1.01 [0.92, 1.12]**
Total events: 834 (LABA/LAMA), 1044 (LAMA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 23.24, df = 24 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 0.27 (P = 0.79)					
Test for subgroup differences: Chi^2 = 0.16, df = 1 (P = 0.69), I^2 =0.0%					



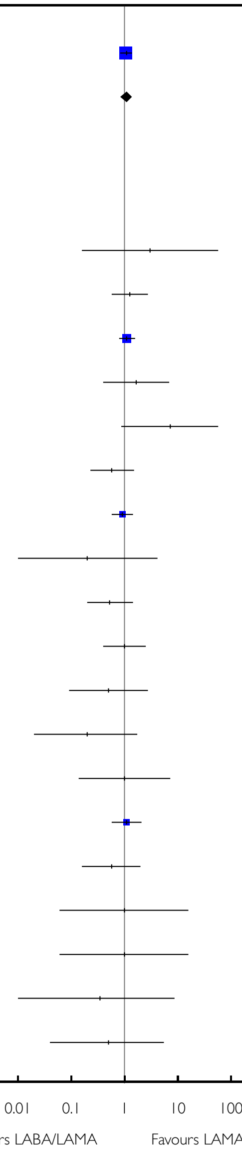
Analysis 2.17. Comparison 2 LABA/LAMA vs LAMA, Outcome 17 COPD SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 17 COPD SAE

Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2013	107/729	203/1477		37.9 %	1.08 [0.84, 1.39]
Subtotal (95% CI)	**729**	**1477**		**37.9 %**	**1.08 [0.84, 1.39]**
Total events: 107 (LABA/LAMA), 203 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.55)					
2 Low-risk					
Asai 2013	4/119	0/39		0.3 %	3.08 [0.16, 58.45]
Bateman 2013	10/474	16/953		3.8 %	1.26 [0.57, 2.80]
Buhl 2015a%b	71/1029	65/1033		20.0 %	1.10 [0.78, 1.56]
Decramer 2014a	5/212	3/208		1.2 %	1.65 [0.39, 7.00]
Decramer 2014b	7/217	1/215		0.5 %	7.13 [0.87, 58.48]
Donohue 2013	7/413	12/418		2.7 %	0.58 [0.23, 1.50]
Hanania 2017	32/1036	45/1341		11.4 %	0.92 [0.58, 1.46]
Kerwin 2017	0/247	2/247		0.3 %	0.20 [0.01, 4.15]
Mahler 2012a	6/570	11/561		2.4 %	0.53 [0.20, 1.45]
Mahler 2012b	9/572	9/570		2.8 %	1.00 [0.39, 2.53]
Mahler 2015a	2/258	4/262		0.8 %	0.50 [0.09, 2.78]
Mahler 2015b	1/250	5/251		0.5 %	0.20 [0.02, 1.70]
Maleki-Yazdi 2014	2/454	2/451		0.6 %	0.99 [0.14, 7.08]
RADIATE 2016	20/407	18/405		5.7 %	1.11 [0.58, 2.13]
Singh 2014	4/385	7/385		1.6 %	0.57 [0.16, 1.95]
Singh 2015a	1/203	1/203		0.3 %	1.00 [0.06, 16.10]
Singh 2015b	1/202	1/203		0.3 %	1.00 [0.06, 16.18]
Tashkin 2009	0/124	1/131		0.2 %	0.35 [0.01, 8.66]
Troosters 2016	1/76	2/76		0.4 %	0.49 [0.04, 5.56]



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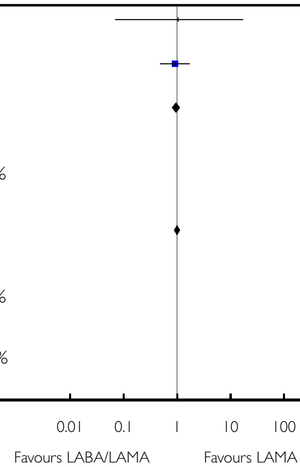
Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Vogelmeier 2008	1/207	1/221		0.3 %	1.07 [0.07, 17.19]
ZuWallack 2014a%b	18/1133	20/1134		5.9 %	0.90 [0.47, 1.71]
Subtotal (95% CI)	**8588**	**9307**		**62.1 %**	**0.96 [0.79, 1.17]**
Total events: 202 (LABA/LAMA), 226 (LAMA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 13.41, df = 20 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 0.39 (P = 0.70)					
Total (95% CI)	**9317**	**10784**		**100.0 %**	**1.00 [0.86, 1.17]**
Total events: 309 (LABA/LAMA), 429 (LAMA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 13.91, df = 21 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 0.06 (P = 0.95)					
Test for subgroup differences: Chi^2 = 0.50, df = 1 (P = 0.48), I^2 =0.0%					



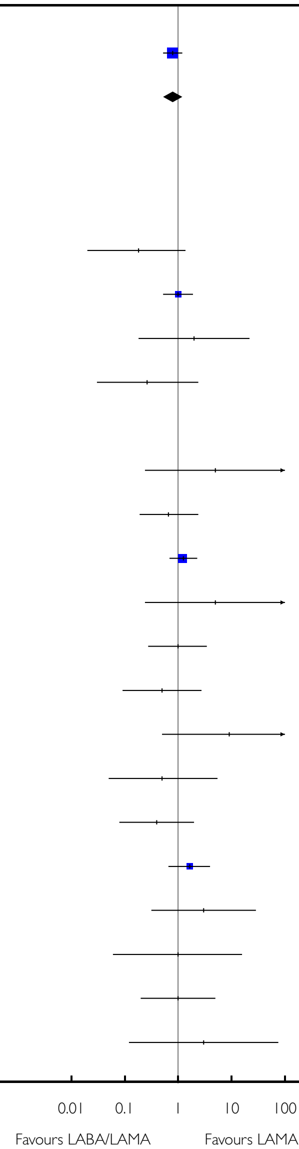
Analysis 2.18. Comparison 2 LABA/LAMA vs LAMA, Outcome 18 Cardiac SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 18 Cardiac SAE

Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2013	33/729	83/1477		32.7 %	0.80 [0.53, 1.20]
Subtotal (95% CI)	**729**	**1477**		**32.7 %**	**0.80 [0.53, 1.20]**
Total events: 33 (LABA/LAMA), 83 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.08 (P = 0.28)					
2 Low-risk					
Bateman 2013	1/474	11/953		1.3 %	0.18 [0.02, 1.41]
Buhl 2015a%b	19/1029	19/1033		13.6 %	1.00 [0.53, 1.91]
D'Urzo 2014	2/335	1/337		1.0 %	2.02 [0.18, 22.36]
D'Urzo 2017	1/182	4/194		1.2 %	0.26 [0.03, 2.37]
Decramer 2014a	0/212	0/208			Not estimable
Decramer 2014b	2/217	0/215		0.6 %	5.00 [0.24, 104.76]
Donohue 2013	4/413	6/418		3.5 %	0.67 [0.19, 2.40]
Hanania 2017	21/1036	22/1341		15.4 %	1.24 [0.68, 2.27]
Kerwin 2017	2/247	0/247		0.6 %	5.04 [0.24, 105.54]
Mahler 2012a	5/570	5/561		3.6 %	0.98 [0.28, 3.42]
Mahler 2012b	2/572	4/570		1.9 %	0.50 [0.09, 2.72]
Mahler 2015a	4/258	0/262		0.7 %	9.28 [0.50, 173.30]
Mahler 2015b	1/250	2/251		1.0 %	0.50 [0.05, 5.55]
Maleki-Yazdi 2014	2/454	5/451		2.1 %	0.39 [0.08, 2.04]
RADIATE 2016	13/407	8/405		7.0 %	1.64 [0.67, 3.99]
Singh 2014	3/385	1/385		1.1 %	3.02 [0.31, 29.12]
Singh 2015a	1/203	1/203		0.7 %	1.00 [0.06, 16.10]
Singh 2015b	3/202	3/203		2.2 %	1.01 [0.20, 5.04]
Troosters 2016	1/76	0/76		0.5 %	3.04 [0.12, 75.80]



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Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Vogelmeier 2008	2/207	3/221		1.7 %	0.71 [0.12, 4.29]
ZuWallack 2014a%b	13/1133	9/1134		7.7 %	1.45 [0.62, 3.41]
Subtotal (95% CI)	**8862**	**9668**		**67.3 %**	**1.09 [0.82, 1.45]**
Total events: 102 (LABA/LAMA), 104 (LAMA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 14.94, df = 19 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 0.59 (P = 0.56)					
Total (95% CI)	**9591**	**11145**		**100.0 %**	**0.98 [0.78, 1.25]**
Total events: 135 (LABA/LAMA), 187 (LAMA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 16.43, df = 20 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 0.14 (P = 0.89)					
Test for subgroup differences: Chi^2 = 1.49, df = 1 (P = 0.22), I^2 =33%					

0.01 0.1 1 10 100

Favours LABA/LAMA Favours LAMA

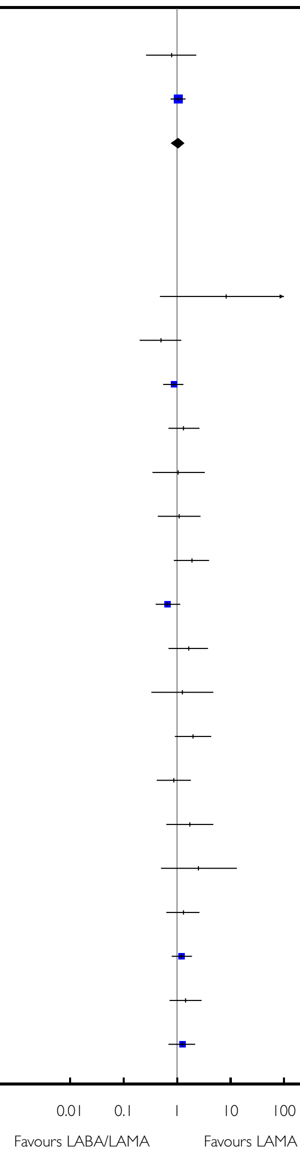
Analysis 2.19. Comparison 2 LABA/LAMA vs LAMA, Outcome 19 Dropouts due to adverse events.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 19 Dropouts due to adverse events

Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Aaron 2007	6/148	8/156		1.6 %	0.78 [0.26, 2.31]
Wedzicha 2013	59/729	114/1477		17.3 %	1.05 [0.76, 1.46]
Subtotal (95% CI)	**877**	**1633**		**18.9 %**	**1.03 [0.75, 1.41]**
Total events: 65 (LABA/LAMA), 122 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.27$, df = 1 (P = 0.61); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.17 (P = 0.87)					
2 Low-risk					
Asai 2013	11/119	0/39		0.2 %	8.37 [0.48, 145.44]
Bateman 2013	6/474	24/953		2.3 %	0.50 [0.20, 1.22]
Buhl 2015a%b	37/1029	43/1033		9.2 %	0.86 [0.55, 1.34]
D'Urzo 2014	21/335	16/337		4.2 %	1.34 [0.69, 2.62]
D'Urzo 2017	6/182	6/194		1.4 %	1.07 [0.34, 3.37]
Decramer 2014a	10/212	9/208		2.2 %	1.09 [0.44, 2.75]
Decramer 2014b	20/217	11/215		3.2 %	1.88 [0.88, 4.03]
Donohue 2013	23/413	34/418		6.2 %	0.67 [0.39, 1.15]
Hanania 2017	12/290	10/389		2.5 %	1.64 [0.70, 3.84]
Kerwin 2017	5/247	4/247		1.1 %	1.26 [0.33, 4.73]
Mahler 2012a	20/570	10/561		3.1 %	2.00 [0.93, 4.32]
Mahler 2012b	14/572	16/570		3.5 %	0.87 [0.42, 1.80]
Mahler 2015a	10/258	6/262		1.8 %	1.72 [0.62, 4.80]
Mahler 2015b	5/250	2/251		0.7 %	2.54 [0.49, 13.22]
Maleki-Yazdi 2014	18/454	14/451		3.7 %	1.29 [0.63, 2.62]
Martinez 2017a	39/526	55/902		10.3 %	1.23 [0.81, 1.89]
Martinez 2017b	23/510	14/439		4.0 %	1.43 [0.73, 2.82]
RADIATE 2016	27/407	22/405		5.5 %	1.24 [0.69, 2.21]



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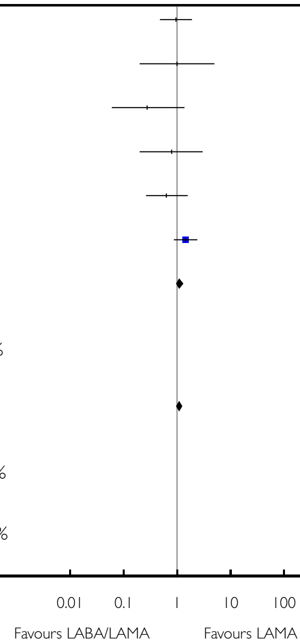
Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Singh 2014	16/385	17/385		3.8 %	0.94 [0.47, 1.89]
Singh 2015a	3/203	3/203		0.7 %	1.00 [0.20, 5.01]
Singh 2015b	2/202	7/203		0.7 %	0.28 [0.06, 1.36]
Troosters 2016	4/76	5/76		1.0 %	0.79 [0.20, 3.06]
Vogelmeier 2008	8/207	13/221		2.3 %	0.64 [0.26, 1.59]
ZuWallack 2014a%b	39/1133	27/1134		7.5 %	1.46 [0.89, 2.40]
Subtotal (95% CI)	**9271**	**10096**		**81.1 %**	**1.12 [0.96, 1.31]**
Total events: 379 (LABA/LAMA), 368 (LAMA)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 23.99$, df = 23 (P = 0.40); $I^2 = 4\%$					
Test for overall effect: Z = 1.46 (P = 0.14)					
Total (95% CI)	**10148**	**11729**		**100.0 %**	**1.10 [0.96, 1.27]**
Total events: 444 (LABA/LAMA), 490 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 24.51$, df = 25 (P = 0.49); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.42 (P = 0.15)					
Test for subgroup differences: $Chi^2 = 0.25$, df = 1 (P = 0.61), $I^2 = 0.0\%$					



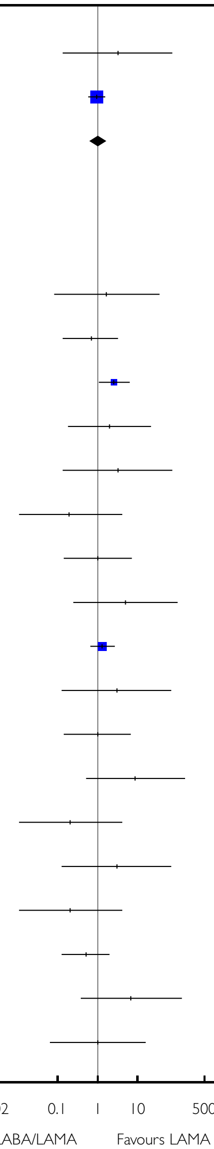
Analysis 2.20. Comparison 2 LABA/LAMA vs LAMA, Outcome 20 Pneumonia.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 2 LABA/LAMA vs LAMA

Outcome: 20 Pneumonia

Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Aaron 2007	1/148	0/156		0.9 %	3.18 [0.13, 78.75]
Wedzicha 2013	23/729	49/1477		36.7 %	0.95 [0.57, 1.57]
Subtotal (95% CI)	**877**	**1633**		**37.6 %**	**0.98 [0.59, 1.61]**
Total events: 24 (LABA/LAMA), 49 (LAMA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.53, df = 1 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 0.09 (P = 0.93)					
2 Low-risk					
Asai 2013	2/119	0/39		1.0 %	1.68 [0.08, 35.77]
Bateman 2013	2/474	6/953		3.6 %	0.67 [0.13, 3.33]
Buhl 2015a%b	18/1029	7/1033		12.1 %	2.61 [1.09, 6.27]
D'Urzo 2014	2/335	1/337		1.6 %	2.02 [0.18, 22.36]
D'Urzo 2017	1/182	0/194		0.9 %	3.21 [0.13, 79.42]
Decramer 2014a	0/212	2/208		1.0 %	0.19 [0.01, 4.07]
Decramer 2014b	2/217	2/215		2.4 %	0.99 [0.14, 7.10]
Donohue 2013	2/413	0/418		1.0 %	5.09 [0.24, 106.24]
Hanania 2017	15/1036	15/1341		18.0 %	1.30 [0.63, 2.67]
Kerwin 2017	1/247	0/247		0.9 %	3.01 [0.12, 74.30]
Mahler 2012a	2/570	2/561		2.4 %	0.98 [0.14, 7.01]
Mahler 2012b	4/572	0/570		1.1 %	9.03 [0.49, 168.14]
Mahler 2015a	0/258	2/262		1.0 %	0.20 [0.01, 4.22]
Mahler 2015b	1/250	0/251		0.9 %	3.02 [0.12, 74.59]
Maleki-Yazdi 2014	0/454	2/451		1.0 %	0.20 [0.01, 4.13]
RADIATE 2016	3/407	6/405		4.8 %	0.49 [0.12, 1.99]
Singh 2014	3/385	0/385		1.1 %	7.05 [0.36, 137.04]
Singh 2015a	1/203	1/203		1.2 %	1.00 [0.06, 16.10]



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Study or subgroup	LABA/LAMA n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Tashkin 2009	0/124	1/131		0.9 %	0.35 [0.01, 8.66]
Troosters 2016	0/76	1/76		0.9 %	0.33 [0.01, 8.20]
Vogelmeier 2008	0/207	0/221			Not estimable
ZuWallack 2014a%b	3/1133	5/1134		4.5 %	0.60 [0.14, 2.51]
Subtotal (95% CI)	**8903**	**9635**		**62.4 %**	**1.23 [0.84, 1.81]**
Total events: 62 (LABA/LAMA), 53 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 16.64$, df = 20 (P = 0.68); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.06 (P = 0.29)					
Total (95% CI)	**9780**	**11268**		**100.0 %**	**1.13 [0.83, 1.53]**
Total events: 86 (LABA/LAMA), 102 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 17.71$, df = 22 (P = 0.72); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.78 (P = 0.43)					
Test for subgroup differences: $Chi^2 = 0.52$, df = 1 (P = 0.47), $I^2 = 0.0\%$					

0.002 0.1 1 10 500

Favours LABA/LAMA Favours LAMA

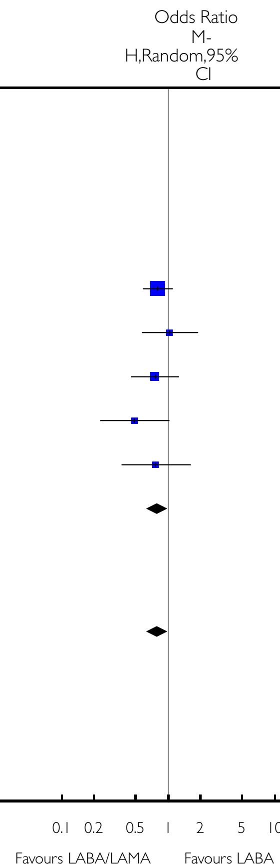
Analysis 3.1. Comparison 3 LABA/LAMA vs LABA, Outcome 1 Moderate to severe exacerbations.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 1 Moderate to severe exacerbations

Study or subgroup	LABA/LAMA n/N	LABA n/N	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk				
Subtotal (95% CI)	**0**	**0**		**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LABA)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Low-risk				
Bateman 2013	85/474	103/476	49.2 %	0.79 [0.57, 1.09]
D'Urzo 2014	24/211	22/198	13.4 %	1.03 [0.56, 1.90]
Donohue 2016a	51/220	33/115	19.3 %	0.75 [0.45, 1.25]
Singh 2014	11/182	23/195	9.0 %	0.48 [0.23, 1.02]
Vogelmeier 2008	13/207	17/210	9.0 %	0.76 [0.36, 1.61]
Subtotal (95% CI)	**1294**	**1194**	**100.0 %**	**0.77 [0.62, 0.97]**
Total events: 184 (LABA/LAMA), 198 (LABA)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.40, df = 4 (P = 0.66); I^2 =0.0%				
Test for overall effect: Z = 2.25 (P = 0.025)				
Total (95% CI)	**1294**	**1194**	**100.0 %**	**0.77 [0.62, 0.97]**
Total events: 184 (LABA/LAMA), 198 (LABA)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.40, df = 4 (P = 0.66); I^2 =0.0%				
Test for overall effect: Z = 2.25 (P = 0.025)				
Test for subgroup differences: Not applicable				



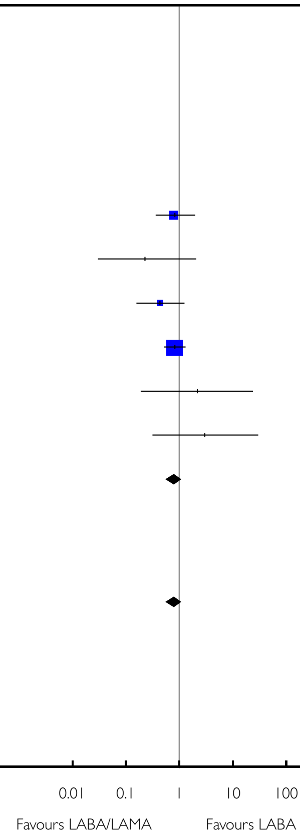
Analysis 3.2. Comparison 3 LABA/LAMA vs LABA, Outcome 2 Severe exacerbations.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 2 Severe exacerbations

Study or subgroup	LABA/LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low-risk					
Bateman 2013	10/474	12/476		17.5 %	0.83 [0.36, 1.95]
D'Urzo 2014	1/211	4/198		2.6 %	0.23 [0.03, 2.08]
Donohue 2016a	7/220	8/115		11.7 %	0.44 [0.16, 1.24]
Ferguson 2016	48/204	56/206		63.6 %	0.82 [0.53, 1.29]
Singh 2014	2/182	1/195		2.2 %	2.16 [0.19, 23.98]
Vogelmeier 2008	3/207	1/210		2.4 %	3.07 [0.32, 29.79]
Subtotal (95% CI)	**1498**	**1400**		**100.0 %**	**0.78 [0.55, 1.12]**
Total events: 71 (LABA/LAMA), 82 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.51$, df = 5 (P = 0.48); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.35 (P = 0.18)					
Total (95% CI)	**1498**	**1400**		**100.0 %**	**0.78 [0.55, 1.12]**
Total events: 71 (LABA/LAMA), 82 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.51$, df = 5 (P = 0.48); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.35 (P = 0.18)					
Test for subgroup differences: Not applicable					



Analysis 3.3. Comparison 3 LABA/LAMA vs LABA, Outcome 3 SGRQ responders at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 3 SGRQ responders at 6 months

Study or subgroup	LABA/LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low-risk					
Bateman 2013	281/441	279/443		16.4 %	1.03 [0.79, 1.36]
Buhl 2015a%b	563/979	427/954		22.1 %	1.67 [1.40, 2.00]
D'Urzo 2014	195/335	174/332		14.7 %	1.26 [0.93, 1.72]
D'Urzo 2017	194/335	164/332		14.7 %	1.41 [1.04, 1.91]
Martinez 2017a	187/503	151/434		16.7 %	1.11 [0.85, 1.45]
Martinez 2017b	139/352	144/430		15.4 %	1.30 [0.97, 1.74]
Subtotal (95% CI)	**2945**	**2925**		**100.0 %**	**1.30 [1.10, 1.53]**
Total events: 1559 (LABA/LAMA), 1339 (LABA)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 11.46$, df = 5 (P = 0.04); I^2 =56%					
Test for overall effect: Z = 3.12 (P = 0.0018)					
Total (95% CI)	**2945**	**2925**		**100.0 %**	**1.30 [1.10, 1.53]**
Total events: 1559 (LABA/LAMA), 1339 (LABA)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 11.46$, df = 5 (P = 0.04); I^2 =56%					
Test for overall effect: Z = 3.12 (P = 0.0018)					
Test for subgroup differences: Not applicable					

0.2 0.5 1 2 5

Favours LABA Favours LABA/LAMA

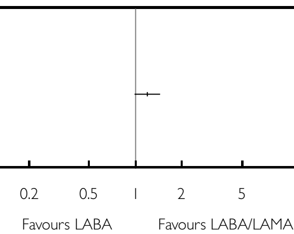
Analysis 3.4. Comparison 3 LABA/LAMA vs LABA, Outcome 4 SGRQ responders at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 4 SGRQ responders at 12 months

Study or subgroup	LABA/LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 High-risk				
2 Low-risk				
Hanania 2017	411/995	314/845		1.19 [0.99, 1.44]



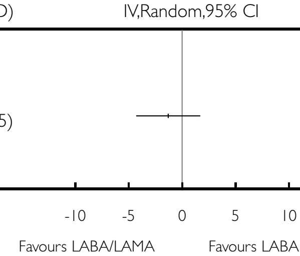
Analysis 3.5. Comparison 3 LABA/LAMA vs LABA, Outcome 5 Change from baseline in SGRQ at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 5 Change from baseline in SGRQ at 3 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 High-risk						
2 Low-risk						
Bateman 2013	474	-9.4 (24.1)	476	-8.11 (23.05)		-1.29 [-4.29, 1.71]



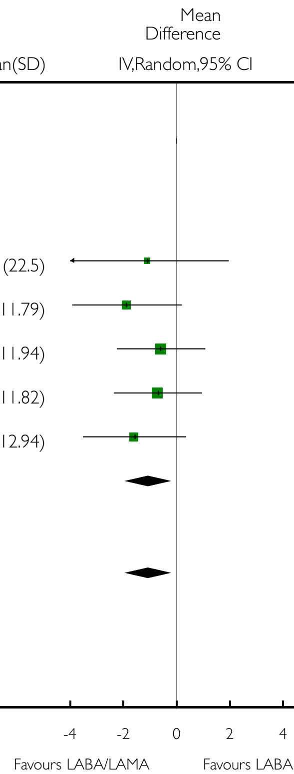
Analysis 3.6. Comparison 3 LABA/LAMA vs LABA, Outcome 6 Change from baseline in SGRQ at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 6 Change from baseline in SGRQ at 6 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA N	Mean(SD)	Weight	Mean Difference IV,Random,95% CI
1 High-risk						
Subtotal (95% CI)	**0**		**0**			**Not estimable**
Heterogeneity: not applicable						
Test for overall effect: not applicable						
2 Low-risk						
Bateman 2013	441	-9.82 (23.7)	443	-8.72 (22.5)	8.1 %	-1.10 [-4.15, 1.95]
D'Urzo 2014	256	-6.57 (11.84)	254	-4.7 (11.79)	17.9 %	-1.87 [-3.92, 0.18]
Martinez 2017a	432	-3.3 (12.06)	371	-2.7 (11.94)	27.2 %	-0.60 [-2.26, 1.06]
Martinez 2017b	430	-3 (11.82)	352	-2.3 (11.82)	27.1 %	-0.70 [-2.37, 0.97]
Singh 2014	338	-7.16 (12.8693)	332	-5.58 (12.94)	19.7 %	-1.58 [-3.53, 0.37]
Subtotal (95% CI)	**1897**		**1752**		**100.0 %**	**-1.09 [-1.96, -0.22]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.34, df = 4 (P = 0.85); I^2 =0.0%						
Test for overall effect: Z = 2.46 (P = 0.014)						
Total (95% CI)	**1897**		**1752**		**100.0 %**	**-1.09 [-1.96, -0.22]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.34, df = 4 (P = 0.85); I^2 =0.0%						
Test for overall effect: Z = 2.46 (P = 0.014)						
Test for subgroup differences: Not applicable						



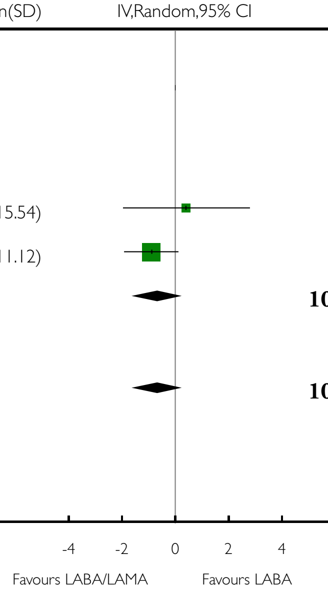
Analysis 3.7. Comparison 3 LABA/LAMA vs LABA, Outcome 7 Change from baseline in SGRQ at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 7 Change from baseline in SGRQ at 12 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
D'Urzo 2017	335	-3.646 (15.76)	332	-4.06 (15.54)		15.7 %	0.41 [-1.96, 2.79]
Hanania 2017	995	-3.3 (11.27)	845	-2.4 (11.12)		84.3 %	-0.90 [-1.93, 0.13]
Subtotal (95% CI)	**1330**		**1177**			**100.0 %**	**-0.69 [-1.64, 0.25]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.99$, df = 1 (P = 0.32); I^2 =0.0%							
Test for overall effect: Z = 1.44 (P = 0.15)							
Total (95% CI)	**1330**		**1177**			**100.0 %**	**-0.69 [-1.64, 0.25]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.99$, df = 1 (P = 0.32); I^2 =0.0%							
Test for overall effect: Z = 1.44 (P = 0.15)							
Test for subgroup differences: Not applicable							



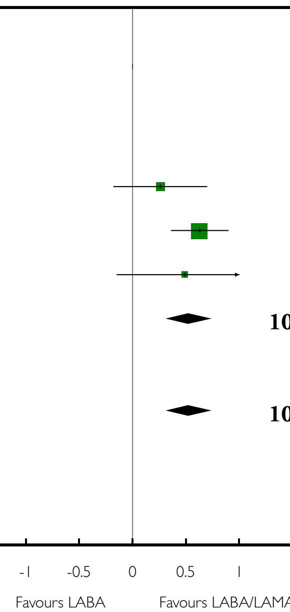
Analysis 3.8. Comparison 3 LABA/LAMA vs LABA, Outcome 8 TDI at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 8 TDI at 3 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Bateman 2013	474	2.44 (3.44)	476	2.18 (3.43)		24.4 %	0.26 [-0.18, 0.70]
Buhl 2015a%b	992	2.136 (3.024)	984	1.51 (3.043)		64.2 %	0.63 [0.36, 0.90]
Vincken 2014	207	2.5 (3.31)	209	2.01 (3.33)		11.5 %	0.49 [-0.15, 1.13]
Subtotal (95% CI)	**1673**		**1669**			**100.0 %**	**0.52 [0.31, 0.74]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.02$, df = 2 (P = 0.36); I^2 =1%							
Test for overall effect: Z = 4.74 (P < 0.00001)							
Total (95% CI)	**1673**		**1669**			**100.0 %**	**0.52 [0.31, 0.74]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.02$, df = 2 (P = 0.36); I^2 =1%							
Test for overall effect: Z = 4.74 (P < 0.00001)							
Test for subgroup differences: Not applicable							



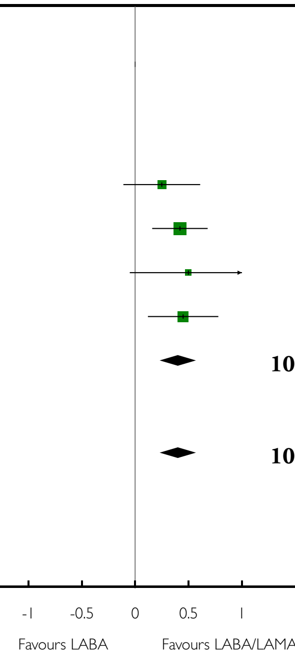
Analysis 3.9. Comparison 3 LABA/LAMA vs LABA, Outcome 9 TDI at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 9 TDI at 6 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Bateman 2013	474	2.72 (2.83)	476	2.47 (2.76)		23.0 %	0.25 [-0.11, 0.61]
Buhl 2015a%b	992	1.98 (2.99)	984	1.56 (3.01)		41.6 %	0.42 [0.16, 0.68]
D'Urzo 2014	260	2.02 (3.2249)	263	1.52 (3.24)		9.5 %	0.50 [-0.05, 1.05]
Singh 2014	344	2.51 (1.11283)	333	2.06 (2.92)		25.9 %	0.45 [0.12, 0.78]
Subtotal (95% CI)	**2070**		**2056**			**100.0 %**	**0.40 [0.23, 0.57]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.91, df = 3 (P = 0.82); I^2 =0.0%							
Test for overall effect: Z = 4.55 (P < 0.00001)							
Total (95% CI)	**2070**		**2056**			**100.0 %**	**0.40 [0.23, 0.57]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.91, df = 3 (P = 0.82); I^2 =0.0%							
Test for overall effect: Z = 4.55 (P < 0.00001)							
Test for subgroup differences: Not applicable							



Analysis 3.10. Comparison 3 LABA/LAMA vs LABA, Outcome 10 TDI at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 10 TDI at 12 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Buhl 2015a%b	992	2.058 (3.118)	984	1.41 (3.168)		37.6 %	0.65 [0.37, 0.92]
D'Urzo 2017	335	1.812 (4.59)	332	1.32 (4.48)		17.2 %	0.49 [-0.20, 1.18]
Hanania 2017	1002	0.5 (1.62)	871	0.3 (1.51)		45.2 %	0.20 [0.06, 0.34]
Subtotal (95% CI)	**2329**		**2187**			**100.0 %**	**0.42 [0.06, 0.77]**
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 8.22$, df = 2 (P = 0.02); I^2 =76%							
Test for overall effect: Z = 2.31 (P = 0.021)							
Total (95% CI)	**2329**		**2187**			**100.0 %**	**0.42 [0.06, 0.77]**
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 8.22$, df = 2 (P = 0.02); I^2 =76%							
Test for overall effect: Z = 2.31 (P = 0.021)							
Test for subgroup differences: Not applicable							

-2 -1 0 1 2

Favours LABA Favours LABA/LAMA

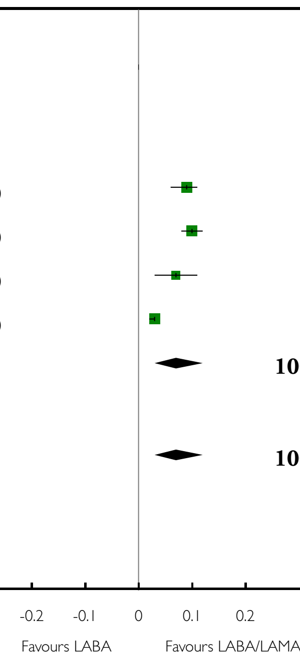
Analysis 3.11. Comparison 3 LABA/LAMA vs LABA, Outcome 11 Change from baseline in FEV1 at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 11 Change from baseline in FEV1 at 3 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Buhl 2015a	521	0.146 (0.205)	519	0.06 (0.205)		25.4 %	0.09 [0.06, 0.11]
Buhl 2015b	497	0.147 (0.201)	503	0.05 (0.202)		25.4 %	0.10 [0.08, 0.12]
Ferguson 2016	192	0.166 (0.219)	199	0.1 (0.221)		21.9 %	0.07 [0.03, 0.11]
Hoshino 2014	18	0.165 (0.013)	20	0.14 (0.0149)		27.3 %	0.03 [0.02, 0.03]
Subtotal (95% CI)	**1228**		**1241**			**100.0 %**	**0.07 [0.03, 0.12]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 48.48$, df = 3 ($P<0.00001$); I^2 =94%							
Test for overall effect: Z = 3.10 (P = 0.0019)							
Total (95% CI)	**1228**		**1241**			**100.0 %**	**0.07 [0.03, 0.12]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 48.48$, df = 3 ($P<0.00001$); I^2 =94%							
Test for overall effect: Z = 3.10 (P = 0.0019)							
Test for subgroup differences: Not applicable							



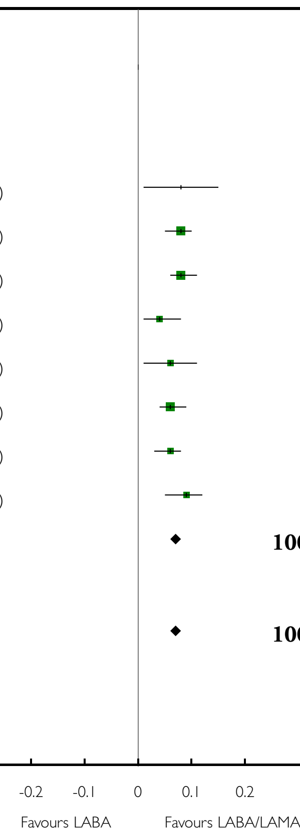
Analysis 3.12. Comparison 3 LABA/LAMA vs LABA, Outcome 12 Change from baseline in FEV1 at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 12 Change from baseline in FEV1 at 6 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Bateman 2013	474	0.17 (0.544)	435	0.09 (0.501)		2.7 %	0.08 [0.01, 0.15]
Buhl 2015a	521	0.112 (0.205)	519	0.03 (0.205)		19.8 %	0.08 [0.05, 0.10]
Buhl 2015b	497	0.119 (0.201)	503	0.03 (0.202)		19.7 %	0.08 [0.06, 0.11]
D'Urzo 2014	271	0.095 (0.19754)	268	0.05 (0.196)		11.1 %	0.05 [0.01, 0.08]
Ferguson 2016	192	0.138 (0.231)	199	0.08 (0.234)		5.8 %	0.06 [0.01, 0.11]
Martinez 2017a	429	0.126 (0.201)	367	0.06 (0.203)		15.5 %	0.06 [0.04, 0.09]
Martinez 2017b	433	0.116 (0.21)	350	0.06 (0.208)		14.2 %	0.06 [0.03, 0.08]
Singh 2014	349	0.083 (0.22418)	337	0 (0.22)		11.1 %	0.09 [0.05, 0.12]
Subtotal (95% CI)	**3166**		**2978**			**100.0 %**	**0.07 [0.06, 0.08]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.32$, df = 7 (P = 0.50); $I^2 = 0.0\%$							
Test for overall effect: Z = 12.40 (P < 0.00001)							
Total (95% CI)	**3166**		**2978**			**100.0 %**	**0.07 [0.06, 0.08]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.32$, df = 7 (P = 0.50); $I^2 = 0.0\%$							
Test for overall effect: Z = 12.40 (P < 0.00001)							
Test for subgroup differences: Not applicable							



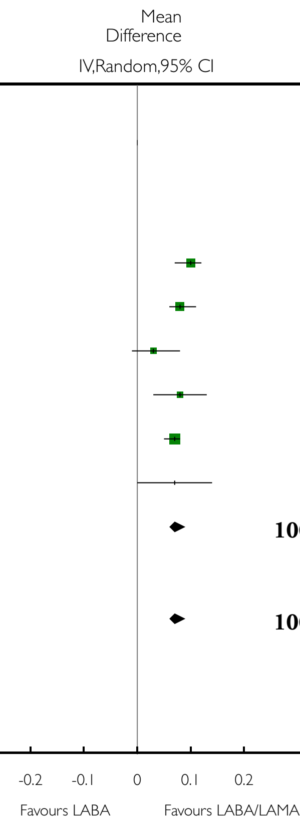
Analysis 3.13. Comparison 3 LABA/LAMA vs LABA, Outcome 13 Change from baseline in FEV1 at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 13 Change from baseline in FEV1 at 12 months

Study or subgroup	LABA/LAMA N	Mean(SD)	LABA N	Mean(SD)	Weight	Mean Difference IV,Random,95% CI
1 High-risk						
Subtotal (95% CI)	**0**		**0**			**Not estimable**
Heterogeneity: not applicable						
Test for overall effect: not applicable						
2 Low-risk						
Buhl 2015a	521	0.099 (0.205)	519	0 (0.205)	21.8 %	0.10 [0.07, 0.12]
Buhl 2015b	497	0.093 (0.201)	503	0.01 (0.202)	21.7 %	0.08 [0.06, 0.11]
D'Urzo 2017	335	0.038 (0.275)	332	0 (0.273)	11.8 %	0.03 [-0.01, 0.08]
Ferguson 2016	192	0.116 (0.234)	199	0.04 (0.238)	10.0 %	0.08 [0.03, 0.13]
Hanania 2017	1021	0.133 (0.179)	871	0.07 (0.181)	29.8 %	0.07 [0.05, 0.08]
NCT01536262 2014	39	0.143 (0.156)	34	0.08 (0.157)	4.9 %	0.07 [0.00, 0.14]
Subtotal (95% CI)	**2605**		**2458**		**100.0 %**	**0.07 [0.06, 0.09]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 9.06, df = 5 (P = 0.11); I^2 =45%						
Test for overall effect: Z = 8.54 (P < 0.00001)						
Total (95% CI)	**2605**		**2458**		**100.0 %**	**0.07 [0.06, 0.09]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 9.06, df = 5 (P = 0.11); I^2 =45%						
Test for overall effect: Z = 8.54 (P < 0.00001)						
Test for subgroup differences: Not applicable						



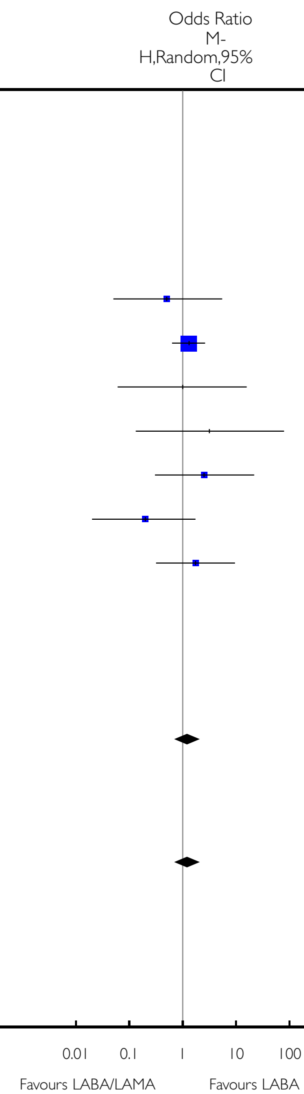
Analysis 3.14. Comparison 3 LABA/LAMA vs LABA, Outcome 14 Mortality.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 14 Mortality

Study or subgroup	LABA/LAMA n/N	LABA n/N	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk				
Subtotal (95% CI)	**0**	**0**		**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LABA)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Low-risk				
Bateman 2013	1/474	2/476	5.4 %	0.50 [0.05, 5.54]
Buhl 2015a%b	18/1029	14/1038	63.2 %	1.30 [0.64, 2.63]
D'Urzo 2014	1/335	1/332	4.1 %	0.99 [0.06, 15.91]
D'Urzo 2017	1/182	0/192	3.0 %	3.18 [0.13, 78.61]
Donohue 2016a	5/392	1/198	6.7 %	2.55 [0.30, 21.94]
Ferguson 2016	1/204	5/206	6.7 %	0.20 [0.02, 1.71]
Hanania 2017	4/1036	2/890	10.8 %	1.72 [0.31, 9.42]
NCT01536262 2014	0/41	0/41		Not estimable
Vincken 2014	0/226	0/221		Not estimable
Vogelmeier 2008	0/207	0/210		Not estimable
Subtotal (95% CI)	**4126**	**3804**	**100.0 %**	**1.19 [0.68, 2.09]**
Total events: 31 (LABA/LAMA), 25 (LABA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.27$, df = 6 (P = 0.64); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.62 (P = 0.54)				
Total (95% CI)	**4126**	**3804**	**100.0 %**	**1.19 [0.68, 2.09]**
Total events: 31 (LABA/LAMA), 25 (LABA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.27$, df = 6 (P = 0.64); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.62 (P = 0.54)				
Test for subgroup differences: Not applicable				



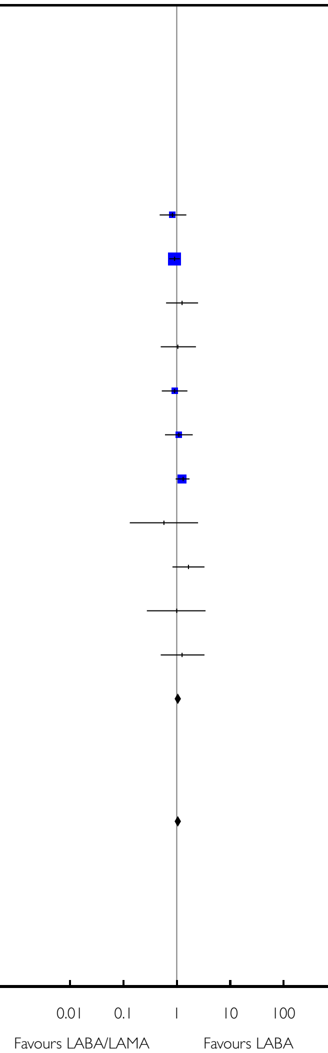
Analysis 3.15. Comparison 3 LABA/LAMA vs LABA, Outcome 15 Total SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 15 Total SAE

Study or subgroup	LABA/LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low-risk					
Bateman 2013	22/474	26/476		6.3 %	0.84 [0.47, 1.51]
Buhl 2015a%b	169/1029	181/1038		40.3 %	0.93 [0.74, 1.17]
D'Urzo 2014	19/335	15/332		4.4 %	1.27 [0.63, 2.55]
D'Urzo 2017	14/182	14/192		3.6 %	1.06 [0.49, 2.29]
Donohue 2016a	38/392	21/198		6.7 %	0.90 [0.52, 1.59]
Ferguson 2016	26/204	24/206		6.1 %	1.11 [0.61, 2.00]
Hanania 2017	114/1036	78/890		23.2 %	1.29 [0.95, 1.74]
NCT01536262 2014	3/41	5/41		0.9 %	0.57 [0.13, 2.55]
Singh 2014	23/385	14/384		4.6 %	1.68 [0.85, 3.31]
Vincken 2014	5/226	5/221		1.4 %	0.98 [0.28, 3.42]
Vogelmeier 2008	10/207	8/210		2.4 %	1.28 [0.50, 3.31]
Subtotal (95% CI)	**4511**	**4188**		**100.0 %**	**1.06 [0.91, 1.22]**
Total events: 443 (LABA/LAMA), 391 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.58$, df = 10 (P = 0.76); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.74 (P = 0.46)					
Total (95% CI)	**4511**	**4188**		**100.0 %**	**1.06 [0.91, 1.22]**
Total events: 443 (LABA/LAMA), 391 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.58$, df = 10 (P = 0.76); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.74 (P = 0.46)					
Test for subgroup differences: Not applicable					



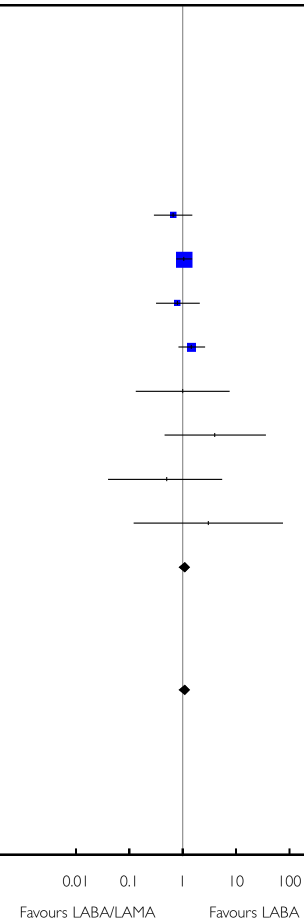
Analysis 3.16. Comparison 3 LABA/LAMA vs LABA, Outcome 16 COPD SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 16 COPD SAE

Study or subgroup	LABA/LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low-risk					
Bateman 2013	10/474	15/476		10.3 %	0.66 [0.29, 1.49]
Buhl 2015a%b	71/1029	67/1038		56.8 %	1.07 [0.76, 1.52]
Ferguson 2016	8/204	10/206		7.5 %	0.80 [0.31, 2.07]
Hanania 2017	32/1036	19/890		20.5 %	1.46 [0.82, 2.60]
NCT01536262 2014	2/41	2/41		1.7 %	1.00 [0.13, 7.46]
Singh 2014	4/385	1/384		1.4 %	4.02 [0.45, 36.14]
Vincken 2014	1/226	2/221		1.2 %	0.49 [0.04, 5.41]
Vogelmeier 2008	1/207	0/210		0.7 %	3.06 [0.12, 75.50]
Subtotal (95% CI)	**3602**	**3466**		**100.0 %**	**1.08 [0.83, 1.40]**
Total events: 129 (LABA/LAMA), 116 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.05$, df = 7 (P = 0.65); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.58 (P = 0.56)					
Total (95% CI)	**3602**	**3466**		**100.0 %**	**1.08 [0.83, 1.40]**
Total events: 129 (LABA/LAMA), 116 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.05$, df = 7 (P = 0.65); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.58 (P = 0.56)					
Test for subgroup differences: Not applicable					



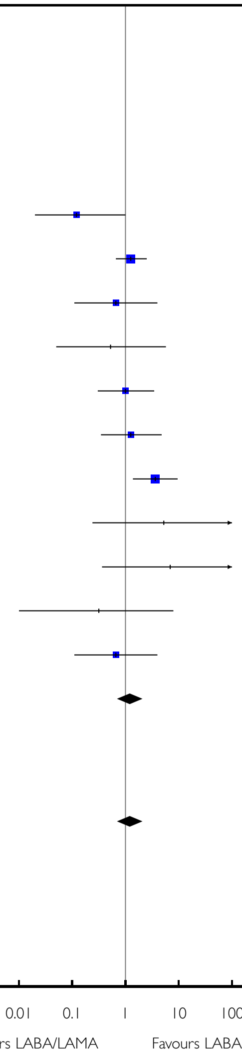
Analysis 3.17. Comparison 3 LABA/LAMA vs LABA, Outcome 17 Cardiac SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 17 Cardiac SAE

Study or subgroup	LABA/LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low-risk					
Bateman 2013	1/474	8/476		5.9 %	0.12 [0.02, 0.99]
Buhl 2015a%b	19/1029	15/1038		23.7 %	1.28 [0.65, 2.54]
D'Urzo 2014	2/335	3/332		7.5 %	0.66 [0.11, 3.97]
D'Urzo 2017	1/182	2/192		4.6 %	0.52 [0.05, 5.84]
Donohue 2016a	8/392	4/198		13.3 %	1.01 [0.30, 3.40]
Ferguson 2016	5/204	4/206		11.7 %	1.27 [0.34, 4.79]
Hanania 2017	21/1036	5/890		17.1 %	3.66 [1.38, 9.75]
NCT01536262 2014	2/41	0/41		3.0 %	5.25 [0.24, 112.88]
Singh 2014	3/385	0/384		3.1 %	7.04 [0.36, 136.69]
Vincken 2014	0/226	1/221		2.7 %	0.32 [0.01, 8.01]
Vogelmeier 2008	2/207	3/210		7.5 %	0.67 [0.11, 4.07]
Subtotal (95% CI)	**4511**	**4188**		**100.0 %**	**1.19 [0.69, 2.07]**
Total events: 64 (LABA/LAMA), 45 (LABA)					
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 13.73$, df = 10 (P = 0.19); $I^2 = 27\%$					
Test for overall effect: Z = 0.63 (P = 0.53)					
Total (95% CI)	**4511**	**4188**		**100.0 %**	**1.19 [0.69, 2.07]**
Total events: 64 (LABA/LAMA), 45 (LABA)					
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 13.73$, df = 10 (P = 0.19); $I^2 = 27\%$					
Test for overall effect: Z = 0.63 (P = 0.53)					
Test for subgroup differences: Not applicable					



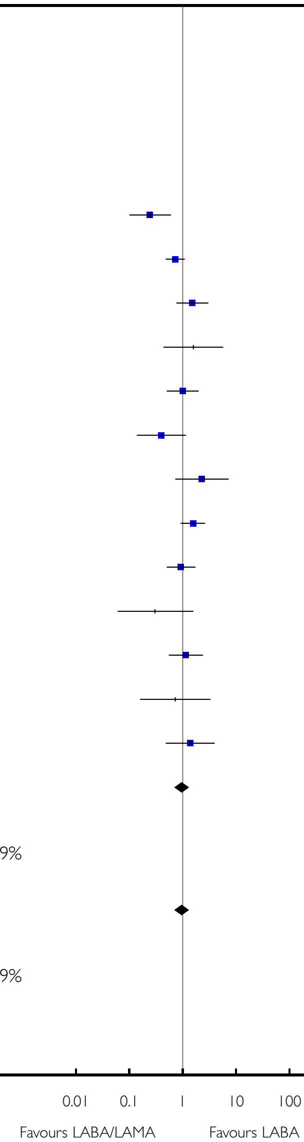
Analysis 3.18. Comparison 3 LABA/LAMA vs LABA, Outcome 18 Dropuouts due to adverse events.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 18 Dropuouts due to adverse events

Study or subgroup	LABA/LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low-risk					
Bateman 2013	6/474	24/476		7.3 %	0.24 [0.10, 0.60]
Buhl 2015a%b	37/1029	51/1038		13.3 %	0.72 [0.47, 1.11]
D'Urzo 2014	21/335	14/332		9.6 %	1.52 [0.76, 3.04]
D'Urzo 2017	6/182	4/192		4.6 %	1.60 [0.44, 5.77]
Donohue 2016a	26/392	13/198		9.7 %	1.01 [0.51, 2.01]
Ferguson 2016	5/204	12/206		6.0 %	0.41 [0.14, 1.17]
Hanania 2017	12/290	4/213		5.4 %	2.26 [0.72, 7.09]
Martinez 2017a	39/526	22/452		11.7 %	1.57 [0.91, 2.68]
Martinez 2017b	23/510	21/438		10.8 %	0.94 [0.51, 1.72]
NCT01536262 2014	2/41	6/41		3.0 %	0.30 [0.06, 1.58]
Singh 2014	16/385	14/384		9.2 %	1.15 [0.55, 2.38]
Vincken 2014	3/226	4/221		3.6 %	0.73 [0.16, 3.30]
Vogelmeier 2016	8/207	6/210		5.9 %	1.37 [0.47, 4.01]
Subtotal (95% CI)	**4801**	**4401**		**100.0 %**	**0.94 [0.68, 1.29]**
Total events: 204 (LABA/LAMA), 195 (LABA)					
Heterogeneity: Tau^2 = 0.15; Chi^2 = 23.45, df = 12 (P = 0.02); I^2 =49%					
Test for overall effect: Z = 0.40 (P = 0.69)					
Total (95% CI)	**4801**	**4401**		**100.0 %**	**0.94 [0.68, 1.29]**
Total events: 204 (LABA/LAMA), 195 (LABA)					
Heterogeneity: Tau^2 = 0.15; Chi^2 = 23.45, df = 12 (P = 0.02); I^2 =49%					
Test for overall effect: Z = 0.40 (P = 0.69)					
Test for subgroup differences: Not applicable					



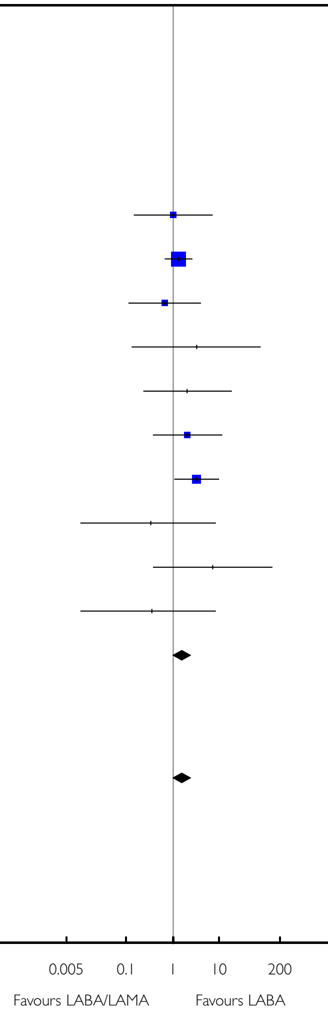
Analysis 3.19. Comparison 3 LABA/LAMA vs LABA, Outcome 19 Pneumonia.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 3 LABA/LAMA vs LABA

Outcome: 19 Pneumonia

Study or subgroup	LABA/LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA/LAMA), 0 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low-risk					
Bateman 2013	2/474	2/476		5.9 %	1.00 [0.14, 7.16]
Buhl 2015a%b	18/1029	14/1038		46.3 %	1.30 [0.64, 2.63]
D'Urzo 2014	2/335	3/332		7.1 %	0.66 [0.11, 3.97]
D'Urzo 2017	1/182	0/192		2.2 %	3.18 [0.13, 78.61]
Donohue 2016a	4/392	1/198		4.7 %	2.03 [0.23, 18.29]
Ferguson 2016	4/204	2/206		7.9 %	2.04 [0.37, 11.26]
Hanania 2017	15/1036	4/890		18.7 %	3.25 [1.08, 9.84]
NCT01536262 2014	0/41	1/41		2.2 %	0.33 [0.01, 8.22]
Singh 2014	3/385	0/384		2.6 %	7.04 [0.36, 136.69]
Vogelmeier 2008	0/207	1/210		2.2 %	0.34 [0.01, 8.31]
Subtotal (95% CI)	**4285**	**3967**		**100.0 %**	**1.54 [0.95, 2.49]**
Total events: 49 (LABA/LAMA), 28 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.17$, df = 9 (P = 0.72); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.76 (P = 0.078)					
Total (95% CI)	**4285**	**3967**		**100.0 %**	**1.54 [0.95, 2.49]**
Total events: 49 (LABA/LAMA), 28 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.17$, df = 9 (P = 0.72); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.76 (P = 0.078)					
Test for subgroup differences: Not applicable					



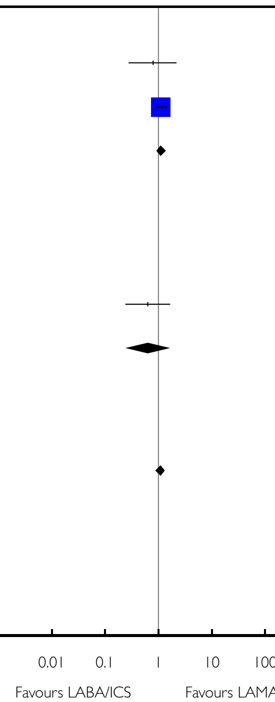
Analysis 4.1. Comparison 4 LABA/ICS vs LAMA, Outcome 1 Moderate to severe exacerbations.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 1 Moderate to severe exacerbations

Study or subgroup	LABA/ICS n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 high-risk					
Pepin 2014	7/127	9/130		4.3 %	0.78 [0.28, 2.17]
Wedzicha 2008	408/658	392/665		91.0 %	1.14 [0.91, 1.42]
Subtotal (95% CI)	**785**	**795**		**95.2 %**	**1.12 [0.90, 1.39]**
Total events: 415 (LABA/ICS), 401 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.49$, df = 1 (P = 0.49); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.01 (P = 0.31)					
2 Low-risk					
Covelli 2016	7/310	11/313		4.8 %	0.63 [0.24, 1.66]
Subtotal (95% CI)	**310**	**313**		**4.8 %**	**0.63 [0.24, 1.66]**
Total events: 7 (LABA/ICS), 11 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.93 (P = 0.35)					
Total (95% CI)	**1095**	**1108**		**100.0 %**	**1.09 [0.88, 1.34]**
Total events: 422 (LABA/ICS), 412 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.76$, df = 2 (P = 0.42); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.79 (P = 0.43)					
Test for subgroup differences: $Chi^2 = 1.27$, df = 1 (P = 0.26), $I^2 = 21\%$					



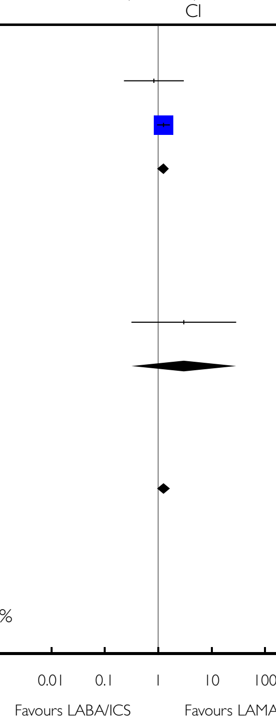
Analysis 4.2. Comparison 4 LABA/ICS vs LAMA, Outcome 2 Severe exacerbations.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 2 Severe exacerbations

Study or subgroup	LABA/ICS n/N	LAMA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 High-risk					
Pepin 2014	4/127	5/130		4.0 %	0.82 [0.23, 2.98]
Wedzicha 2008	105/658	84/665		94.7 %	1.26 [0.97, 1.65]
Subtotal (95% CI)	**785**	**795**		**98.7 %**	**1.24 [0.96, 1.61]**
Total events: 109 (LABA/ICS), 89 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.42$, df = 1 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 1.63 (P = 0.10)					
2 Low-risk					
Covelli 2016	3/310	1/313		1.3 %	3.03 [0.32, 28.96]
Subtotal (95% CI)	**310**	**313**		**1.3 %**	**3.03 [0.32, 28.96]**
Total events: 3 (LABA/ICS), 1 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.96 (P = 0.34)					
Total (95% CI)	**1095**	**1108**		**100.0 %**	**1.26 [0.97, 1.63]**
Total events: 112 (LABA/ICS), 90 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.01$, df = 2 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 1.73 (P = 0.084)					
Test for subgroup differences: $Chi^2 = 0.59$, df = 1 (P = 0.44), I^2 =0.0%					



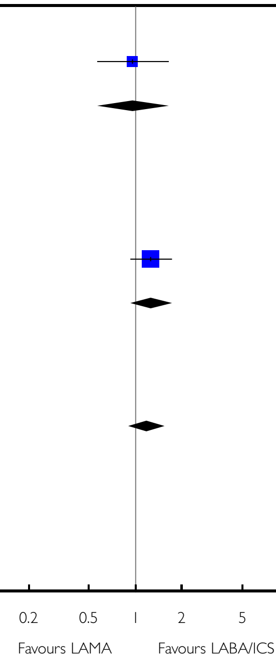
Analysis 4.3. Comparison 4 LABA/ICS vs LAMA, Outcome 3 SGRQ responders at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 3 SGRQ responders at 3 months

Study or subgroup	LABA/ICS n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Pepin 2014	52/106	54/108		26.3 %	0.96 [0.56, 1.65]
Subtotal (95% CI)	**106**	**108**		**26.3 %**	**0.96 [0.56, 1.65]**
Total events: 52 (LABA/ICS), 54 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.14 (P = 0.89)					
2 Low-risk					
Covelli 2016	145/304	128/305		73.7 %	1.26 [0.92, 1.74]
Subtotal (95% CI)	**304**	**305**		**73.7 %**	**1.26 [0.92, 1.74]**
Total events: 145 (LABA/ICS), 128 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.42 (P = 0.16)					
Total (95% CI)	**410**	**413**		**100.0 %**	**1.17 [0.89, 1.55]**
Total events: 197 (LABA/ICS), 182 (LAMA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.72, df = 1 (P = 0.40); I^2 =0.0%					
Test for overall effect: Z = 1.15 (P = 0.25)					
Test for subgroup differences: Chi^2 = 0.72, df = 1 (P = 0.40), I^2 =0.0%					



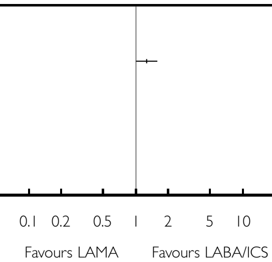
Analysis 4.4. Comparison 4 LABA/ICS vs LAMA, Outcome 4 SGRQ responders at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 4 SGRQ responders at 6 months

Study or subgroup	LABA/ICS n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 High-risk				
Wedzicha 2008	211/603	190/633		1.26 [0.99, 1.59]
2 Low-risk				



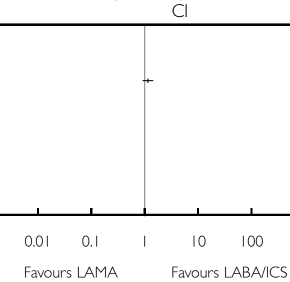
Analysis 4.5. Comparison 4 LABA/ICS vs LAMA, Outcome 5 SGRQ responders at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 5 SGRQ responders at 12 months

Study or subgroup	LABA/ICS n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 High-risk				
Wedzicha 2008	194/606	180/621		1.15 [0.90, 1.47]
2 Low-risk				



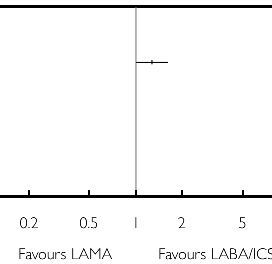
Analysis 4.6. Comparison 4 LABA/ICS vs LAMA, Outcome 6 SGRQ responder at 2 years.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 6 SGRQ responder at 2 years

Study or subgroup	LABA/ICS n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 High-risk				
Wedzicha 2008	193/603	169/626		1.27 [1.00, 1.63]
2 Low-risk				



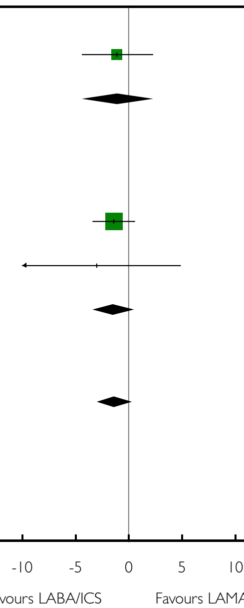
Analysis 4.7. Comparison 4 LABA/ICS vs LAMA, Outcome 7 Change from baseline in SGRQ at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 7 Change from baseline in SGRQ at 3 months

Study or subgroup	LABA/ICS N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Pepin 2014	106	-6.03 (13.24)	108	-4.97 (11.5)		25.2 %	-1.06 [-4.39, 2.27]
Subtotal (95% CI)	**106**		**108**			**25.2 %**	**-1.06 [-4.39, 2.27]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.62 (P = 0.53)							
2 Low-risk							
Covelli 2016	274	-3.9 (11.77)	259	-2.52 (11.68)		70.3 %	-1.38 [-3.37, 0.61]
Perng 2009	33	-12 (19.05)	34	-9 (13.39)		4.5 %	-3.00 [-10.91, 4.91]
Subtotal (95% CI)	**307**		**293**			**74.8 %**	**-1.48 [-3.41, 0.45]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.15$, df = 1 (P = 0.70); I^2 =0.0%							
Test for overall effect: Z = 1.50 (P = 0.13)							
Total (95% CI)	**413**		**401**			**100.0 %**	**-1.37 [-3.04, 0.30]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.20$, df = 2 (P = 0.91); I^2 =0.0%							
Test for overall effect: Z = 1.61 (P = 0.11)							
Test for subgroup differences: $Chi^2 = 0.05$, df = 1 (P = 0.83), I^2 =0.0%							



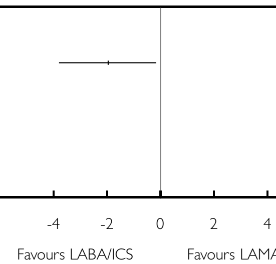
Analysis 4.8. Comparison 4 LABA/ICS vs LAMA, Outcome 8 Change from baseline in SGRQ at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 8 Change from baseline in SGRQ at 6 months

Study or subgroup	LABA/ICS N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 High-risk						
Wedzicha 2008	493	-2.42 (14.62)	506	-0.45 (14.69)		-1.97 [-3.79, -0.15]
2 Low-risk						



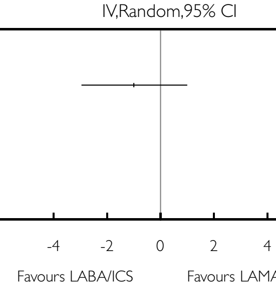
Analysis 4.9. Comparison 4 LABA/ICS vs LAMA, Outcome 9 Change from baseline in SGRQ at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 9 Change from baseline in SGRQ at 12 months

Study or subgroup	LABA/ICS N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 High-risk						
Wedzicha 2008	433	-2.55 (15.19)	414	-1.56 (14.32)		-0.99 [-2.98, 1.00]
2 Low-risk						



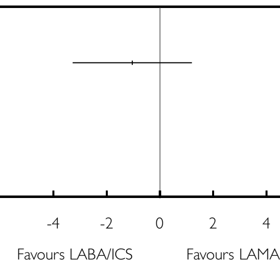
Analysis 4.10. Comparison 4 LABA/ICS vs LAMA, Outcome 10 Change from baseline in SGRQ at 2 years.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 10 Change from baseline in SGRQ at 2 years

Study or subgroup	LABA/ICS N	LABA/ICS Mean(SD)	LAMA N	LAMA Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 High-risk						
Wedzicha 2008	377	-2.81 (16.35)	353	-1.77 (14.61)		-1.04 [-3.29, 1.21]
2 Low-risk						



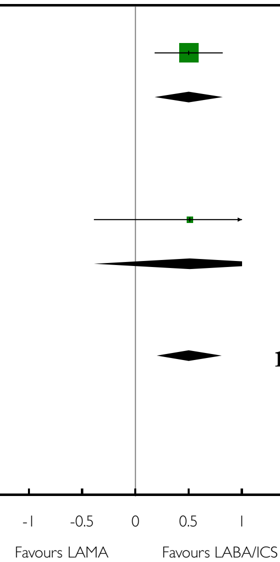
Analysis 4.11. Comparison 4 LABA/ICS vs LAMA, Outcome 11 TDI at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 11 TDI at 3 months

Study or subgroup	LABA/ICS N	LABA/ICS Mean(SD)	LAMA N	LAMA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2008	599	0.7 (2.81)	599	0.2 (2.9)		88.6 %	0.50 [0.18, 0.82]
Subtotal (95% CI)	**599**		**599**			**88.6 %**	**0.50 [0.18, 0.82]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.03 (P = 0.0024)							
2 Low-risk							
SCO40034 2005	61	0.459 (2.579)	64	-0.05 (2.559)		11.4 %	0.51 [-0.39, 1.41]
Subtotal (95% CI)	**61**		**64**			**11.4 %**	**0.51 [-0.39, 1.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.10 (P = 0.27)							
Total (95% CI)	**660**		**663**			**100.0 %**	**0.50 [0.20, 0.81]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.99); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.23 (P = 0.0013)							
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.99), $I^2 = 0.0\%$							



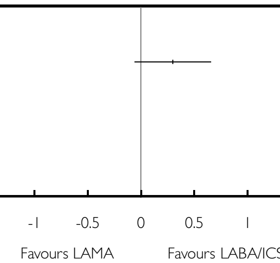
Analysis 4.12. Comparison 4 LABA/ICS vs LAMA, Outcome 12 TDI at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 12 TDI at 6 months

Study or subgroup	LABA/ICS N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 High-risk						
Wedzicha 2008	561	0.8 (3.03)	542	0.5 (3.09)		0.30 [-0.06, 0.66]
2 Low-risk						



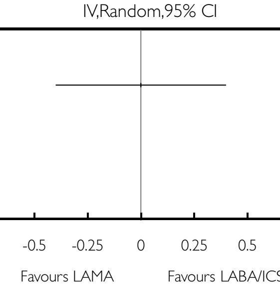
Analysis 4.13. Comparison 4 LABA/ICS vs LAMA, Outcome 13 TDI at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 13 TDI at 12 months

Study or subgroup	LABA/ICS N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 High-risk						
Wedzicha 2008	491	1.1 (3.3)	451	1.1 (2.97)		0.0 [-0.40, 0.40]
2 Low-risk						



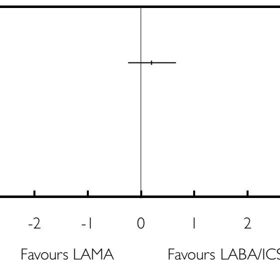
Analysis 4.14. Comparison 4 LABA/ICS vs LAMA, Outcome 14 TDI at 2 years.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 14 TDI at 2 years

Study or subgroup	LABA/ICS N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 High-risk						
Wedzicha 2008	428	1.4 (3.28)	386	1.2 (3.22)		0.20 [-0.25, 0.65]
2 Low-risk						



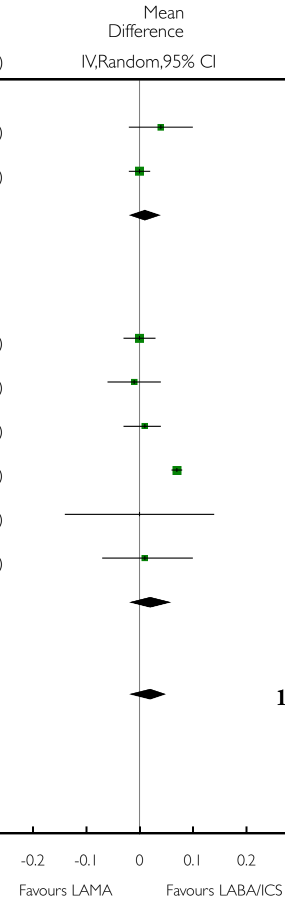
Analysis 4.15. Comparison 4 LABA/ICS vs LAMA, Outcome 15 Change from baseline in FEV1 at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 15 Change from baseline in FEV1 at 3 months

Study or subgroup	LABA/ICS N	LABA/ICS Mean(SD)	LAMA N	LAMA Mean(SD)	Weight	Mean Difference IV,Random,95% CI
1 High-risk						
Pepin 2014	112	0.117 (0.234)	112	0.08 (0.232)	11.3 %	0.04 [-0.02, 0.10]
Wedzicha 2008	547	0.02 (0.208)	582	0.02 (0.218)	16.0 %	0.0 [-0.02, 0.02]
Subtotal (95% CI)	**659**		**694**		**27.3 %**	**0.01 [-0.02, 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 1 (P = 0.27); I² =17%						
Test for overall effect: Z = 0.51 (P = 0.61)						
2 Low-risk						
Cazzola 2007	26	0.14 (0.056)	26	0.14 (0.066)	15.0 %	0.00 [-0.03, 0.03]
COSMOS-J 2016	120	-0.007 (0.2069)	114	0 (0.1893)	12.7 %	-0.01 [-0.06, 0.04]
Covelli 2016	268	0.098 (0.218)	249	0.09 (0.221)	14.4 %	0.01 [-0.03, 0.04]
Hoshino 2013	16	0.115 (0.018)	15	0.04 (0.012)	17.2 %	0.07 [0.06, 0.08]
Perng 2009	33	0.129 (0.322)	34	0.13 (0.239)	4.7 %	0.00 [-0.14, 0.14]
SCO40034 2005	61	0.248 (0.237)	64	0.23 (0.235)	8.7 %	0.01 [-0.07, 0.10]
Subtotal (95% CI)	**524**		**502**		**72.7 %**	**0.02 [-0.02, 0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 33.66, df = 5 (P<0.00001); I² =85%						
Test for overall effect: Z = 0.81 (P = 0.42)						
Total (95% CI)	**1183**		**1196**		**100.0 %**	**0.02 [-0.02, 0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 51.33, df = 7 (P<0.00001); I² =86%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² =0.0%						



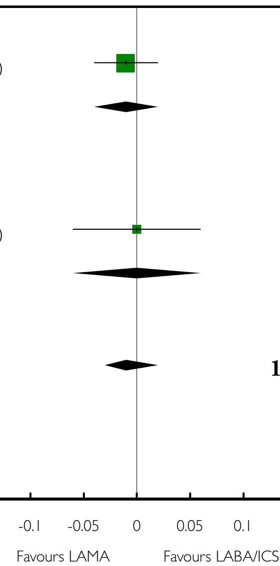
Analysis 4.16. Comparison 4 LABA/ICS vs LAMA, Outcome 16 Change from baseline in FEV1 at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 16 Change from baseline in FEV1 at 6 months

Study or subgroup	LABA/ICS N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Wedzicha 2008	547	0.01 (0.223)	524	0.02 (0.228)		83.2 %	-0.01 [-0.04, 0.02]
Subtotal (95% CI)	**547**		**524**			**83.2 %**	**-0.01 [-0.04, 0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.73 (P = 0.47)							
2 Low-risk							
COSMOS-J 2016	117	-0.019 (0.2293)	113	-0.02 (0.2355)		16.8 %	0.00 [-0.06, 0.06]
Subtotal (95% CI)	**117**		**113**			**16.8 %**	**0.00 [-0.06, 0.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.07 (P = 0.95)							
Total (95% CI)	**664**		**637**			**100.0 %**	**-0.01 [-0.03, 0.02]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.06$, df = 1 (P = 0.81); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.69 (P = 0.49)							
Test for subgroup differences: $Chi^2 = 0.06$, df = 1 (P = 0.81), $I^2 = 0.0\%$							



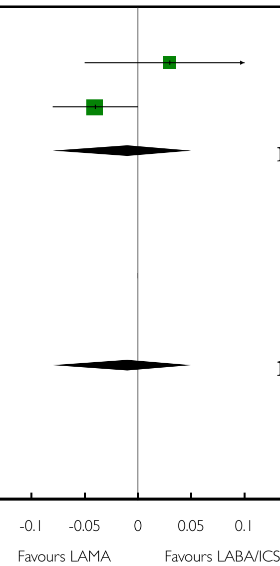
Analysis 4.17. Comparison 4 LABA/ICS vs LAMA, Outcome 17 Change from baseline in FEV1 at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 17 Change from baseline in FEV1 at 12 months

Study or subgroup	LABA/ICS N	Mean(SD)	LAMA N	Mean(SD)	Weight	Mean Difference IV,Random,95% CI
1 High-risk						
Sarac 2016	22	0.04 (0.188)	22	0.01 (0.047)	36.0 %	0.03 [-0.05, 0.11]
Wedzicha 2008	469	-0.02 (0.269)	420	0.02 (0.274)	64.0 %	-0.04 [-0.08, 0.00]
Subtotal (95% CI)	**491**		**442**		**100.0 %**	**-0.01 [-0.08, 0.05]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.40, df = 1 (P = 0.12); I^2 =58%						
Test for overall effect: Z = 0.44 (P = 0.66)						
2 Low-risk						
Subtotal (95% CI)	**0**		**0**			**Not estimable**
Heterogeneity: not applicable						
Test for overall effect: not applicable						
Total (95% CI)	**491**		**442**		**100.0 %**	**-0.01 [-0.08, 0.05]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.40, df = 1 (P = 0.12); I^2 =58%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Test for subgroup differences: Not applicable						



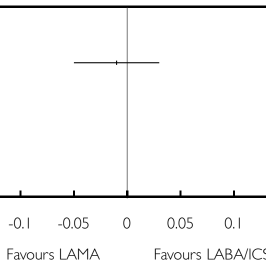
Analysis 4.18. Comparison 4 LABA/ICS vs LAMA, Outcome 18 Change from baseline in FEV1 at 2 years.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 18 Change from baseline in FEV1 at 2 years

Study or subgroup	LABA/ICS N	Mean(SD)	LAMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 High-risk						
Wedzicha 2008	414	-0.03 (0.242)	372	-0.02 (0.276)		-0.01 [-0.05, 0.03]
2 Low-risk						



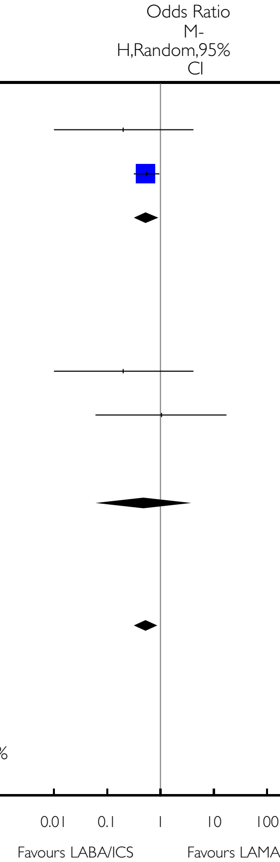
Analysis 4.19. Comparison 4 LABA/ICS vs LAMA, Outcome 19 Mortality.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 19 Mortality

Study or subgroup	LABA/ICS n/N	LAMA n/N	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk				
Pepin 2014	0/127	2/130	2.9 %	0.20 [0.01, 4.24]
Wedzicha 2008	21/658	38/665	90.8 %	0.54 [0.32, 0.94]
Subtotal (95% CI)	**785**	**795**	**93.7 %**	**0.53 [0.31, 0.90]**
Total events: 21 (LABA/ICS), 40 (LAMA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.40$, df = 1 (P = 0.53); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.34 (P = 0.019)				
2 Low-risk				
Covelli 2016	0/310	2/313	2.9 %	0.20 [0.01, 4.20]
Perng 2009	1/33	1/34	3.4 %	1.03 [0.06, 17.20]
SCO40034 2005	0/61	0/64		Not estimable
Subtotal (95% CI)	**404**	**411**	**6.3 %**	**0.48 [0.06, 3.82]**
Total events: 1 (LABA/ICS), 3 (LAMA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.61$, df = 1 (P = 0.43); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.69 (P = 0.49)				
Total (95% CI)	**1189**	**1206**	**100.0 %**	**0.52 [0.31, 0.88]**
Total events: 22 (LABA/ICS), 43 (LAMA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.01$, df = 3 (P = 0.80); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.44 (P = 0.015)				
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.94), $I^2 = 0.0\%$				



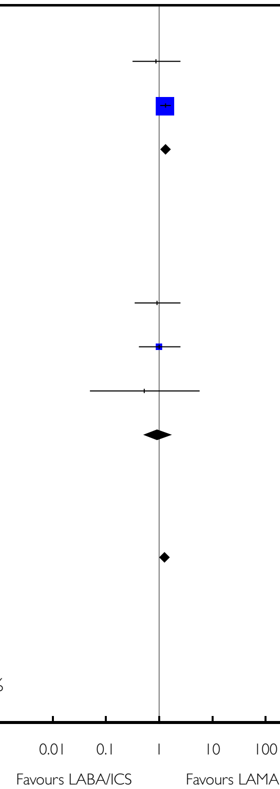
Analysis 4.20. Comparison 4 LABA/ICS vs LAMA, Outcome 20 Total SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 20 Total SAE

Study or subgroup	LABA/ICS n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Pepin 2014	7/127	8/130		4.3 %	0.89 [0.31, 2.53]
Wedzicha 2008	215/658	179/665		84.3 %	1.32 [1.04, 1.67]
Subtotal (95% CI)	**785**	**795**		**88.7 %**	**1.29 [1.03, 1.63]**
Total events: 222 (LABA/ICS), 187 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.52$, df = 1 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 2.18 (P = 0.029)					
2 Low-risk					
COSMOS-J 2016	8/136	8/126		4.6 %	0.92 [0.34, 2.53]
Covelli 2016	10/310	10/313		5.9 %	1.01 [0.41, 2.46]
SCO40034 2005	1/61	2/64		0.8 %	0.52 [0.05, 5.85]
Subtotal (95% CI)	**507**	**503**		**11.3 %**	**0.93 [0.49, 1.77]**
Total events: 19 (LABA/ICS), 20 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.26$, df = 2 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 0.23 (P = 0.82)					
Total (95% CI)	**1292**	**1298**		**100.0 %**	**1.25 [1.00, 1.55]**
Total events: 241 (LABA/ICS), 207 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.67$, df = 4 (P = 0.80); I^2 =0.0%					
Test for overall effect: Z = 1.98 (P = 0.048)					
Test for subgroup differences: $Chi^2 = 0.90$, df = 1 (P = 0.34), I^2 =0.0%					



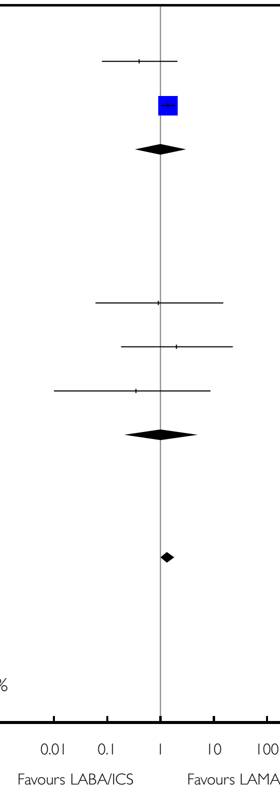
Analysis 4.21. Comparison 4 LABA/ICS vs LAMA, Outcome 21 COPD SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 21 COPD SAE

Study or subgroup	LABA/ICS n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Pepin 2014	2/127	5/130		3.1 %	0.40 [0.08, 2.10]
Wedzicha 2008	113/658	86/665		93.4 %	1.40 [1.03, 1.89]
Subtotal (95% CI)	**785**	**795**		**96.6 %**	**0.99 [0.33, 2.96]**
Total events: 115 (LABA/ICS), 91 (LAMA)					
Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 2.11$, df = 1 (P = 0.15); I^2 =53%					
Test for overall effect: Z = 0.03 (P = 0.98)					
2 Low-risk					
COSMOS-J 2016	1/136	1/126		1.1 %	0.93 [0.06, 14.96]
Covelli 2016	2/310	1/313		1.5 %	2.03 [0.18, 22.46]
SCO40034 2005	0/61	1/64		0.8 %	0.34 [0.01, 8.61]
Subtotal (95% CI)	**507**	**503**		**3.4 %**	**1.02 [0.21, 4.99]**
Total events: 3 (LABA/ICS), 3 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.76$, df = 2 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 0.03 (P = 0.98)					
Total (95% CI)	**1292**	**1298**		**100.0 %**	**1.33 [0.99, 1.78]**
Total events: 118 (LABA/ICS), 94 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.98$, df = 4 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 1.89 (P = 0.058)					
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.97), I^2 =0.0%					



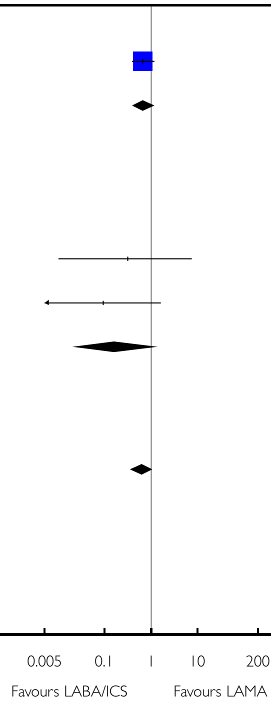
Analysis 4.22. Comparison 4 LABA/ICS vs LAMA, Outcome 22 Cardiac SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 22 Cardiac SAE

Study or subgroup	LABA/ICS n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Wedzicha 2008	23/658	34/665		93.0 %	0.67 [0.39, 1.15]
Subtotal (95% CI)	**658**	**665**		**93.0 %**	**0.67 [0.39, 1.15]**
Total events: 23 (LABA/ICS), 34 (LAMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.44 (P = 0.15)					
2 Low-risk					
COSMOS-J 2016	0/136	1/126		3.2 %	0.31 [0.01, 7.59]
Covelli 2016	0/310	5/313		3.9 %	0.09 [0.00, 1.64]
Subtotal (95% CI)	**446**	**439**		**7.0 %**	**0.16 [0.02, 1.34]**
Total events: 0 (LABA/ICS), 6 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.32$, df = 1 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.69 (P = 0.091)					
Total (95% CI)	**1104**	**1104**		**100.0 %**	**0.61 [0.34, 1.08]**
Total events: 23 (LABA/ICS), 40 (LAMA)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 2.03$, df = 2 (P = 0.36); $I^2 = 1\%$					
Test for overall effect: Z = 1.71 (P = 0.087)					
Test for subgroup differences: $Chi^2 = 1.66$, df = 1 (P = 0.20), $I^2 = 40\%$					



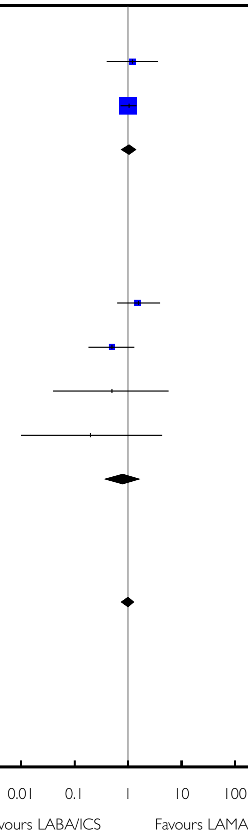
Analysis 4.23. Comparison 4 LABA/ICS vs LAMA, Outcome 23 Dropouts due to adverse events.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 23 Dropouts due to adverse events

Study or subgroup	LABA/ICS n/N	LAMA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Pepin 2014	7/127	6/130		7.2 %	1.21 [0.39, 3.69]
Wedzicha 2008	67/658	66/665		70.4 %	1.03 [0.72, 1.47]
Subtotal (95% CI)	**785**	**795**		**77.6 %**	**1.04 [0.74, 1.47]**
Total events: 74 (LABA/ICS), 72 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.07$, df = 1 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 0.25 (P = 0.80)					
2 Low-risk					
COSMOS-J 2016	13/136	8/126		10.8 %	1.56 [0.62, 3.90]
Covelli 2016	6/310	12/313		9.2 %	0.50 [0.18, 1.34]
Perng 2009	1/33	2/34		1.5 %	0.50 [0.04, 5.79]
SCO40034 2005	0/61	2/64		1.0 %	0.20 [0.01, 4.32]
Subtotal (95% CI)	**540**	**537**		**22.4 %**	**0.78 [0.35, 1.71]**
Total events: 20 (LABA/ICS), 24 (LAMA)					
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 3.84$, df = 3 (P = 0.28); I^2 =22%					
Test for overall effect: Z = 0.62 (P = 0.53)					
Total (95% CI)	**1325**	**1332**		**100.0 %**	**0.99 [0.73, 1.34]**
Total events: 94 (LABA/ICS), 96 (LAMA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.31$, df = 5 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 0.06 (P = 0.95)					
Test for subgroup differences: $Chi^2 = 0.45$, df = 1 (P = 0.50), I^2 =0.0%					



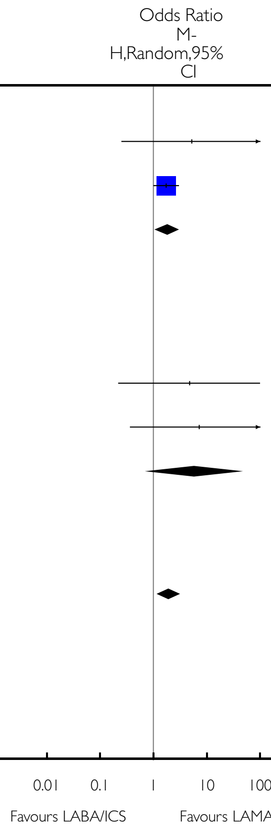
Analysis 4.24. Comparison 4 LABA/ICS vs LAMA, Outcome 24 Pneumonia.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 4 LABA/ICS vs LAMA

Outcome: 24 Pneumonia

Study or subgroup	LABA/ICS n/N	LAMA n/N	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk				
Pepin 2014	2/127	0/130	2.9 %	5.20 [0.25, 109.37]
Wedzicha 2008	37/658	22/665	91.3 %	1.74 [1.02, 2.99]
Subtotal (95% CI)	**785**	**795**	**94.1 %**	**1.80 [1.06, 3.06]**
Total events: 39 (LABA/ICS), 22 (LAMA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.48$, df = 1 (P = 0.49); I^2 =0.0%				
Test for overall effect: Z = 2.17 (P = 0.030)				
2 Low-risk				
COSMOS-J 2016	2/136	0/126	2.9 %	4.70 [0.22, 98.91]
Covelli 2016	3/310	0/313	3.0 %	7.14 [0.37, 138.74]
Subtotal (95% CI)	**446**	**439**	**5.9 %**	**5.82 [0.70, 48.80]**
Total events: 5 (LABA/ICS), 0 (LAMA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.04$, df = 1 (P = 0.85); I^2 =0.0%				
Test for overall effect: Z = 1.62 (P = 0.10)				
Total (95% CI)	**1231**	**1234**	**100.0 %**	**1.93 [1.15, 3.23]**
Total events: 44 (LABA/ICS), 22 (LAMA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.64$, df = 3 (P = 0.65); I^2 =0.0%				
Test for overall effect: Z = 2.50 (P = 0.012)				
Test for subgroup differences: $Chi^2 = 1.10$, df = 1 (P = 0.29), I^2 =9%				



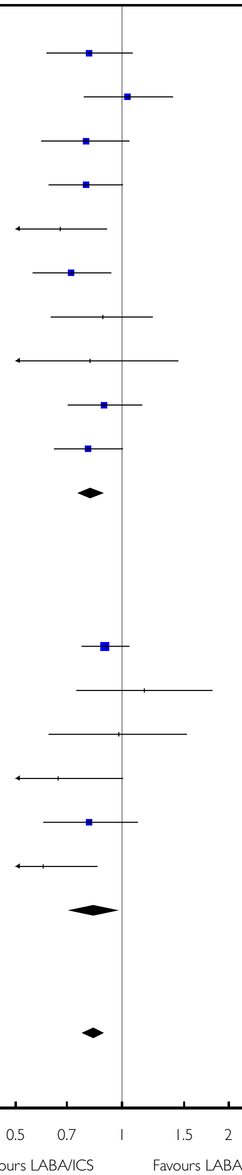
Analysis 5.1. Comparison 5 LABA/ICS vs LABA, Outcome 1 Moderate to severe exacerbations.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 1 Moderate to severe exacerbations

Study or subgroup	LABA/ICS n/N	LABA n/N	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk				
Anzueto 2009	208/394	234/403	6.2 %	0.81 [0.61, 1.07]
Calverley 2003 TRISTAN	193/358	197/372	5.7 %	1.04 [0.78, 1.39]
Ferguson 2008	211/391	230/385	6.0 %	0.79 [0.59, 1.05]
Ferguson 2017	171/606	204/613	8.2 %	0.79 [0.62, 1.01]
Fukuchi 2013	76/636	111/657	4.9 %	0.67 [0.49, 0.91]
Kardos 2007	210/507	241/487	7.7 %	0.72 [0.56, 0.93]
Ohar 2014	102/314	115/325	4.5 %	0.88 [0.63, 1.22]
SCO40041 2008	49/92	55/94	1.4 %	0.81 [0.45, 1.44]
Sharafkhaneh 2012	342/807	182/403	8.4 %	0.89 [0.70, 1.14]
Wedzicha 2014	264/601	294/596	9.4 %	0.80 [0.64, 1.01]
Subtotal (95% CI)	**4706**	**4335**	**62.5 %**	**0.81 [0.75, 0.89]**
Total events: 1826 (LABA/ICS), 1863 (LABA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.02$, df = 9 (P = 0.74); $I^2 = 0.0\%$				
Test for overall effect: Z = 4.57 (P < 0.00001)				
2 Low-risk				
Calverley 2007	1039/1533	1065/1521	20.7 %	0.90 [0.77, 1.05]
Hanania 2003	61/178	55/177	2.5 %	1.16 [0.74, 1.80]
Mahler 2002	61/165	60/160	2.4 %	0.98 [0.62, 1.53]
Rossi 2014	44/288	63/293	2.7 %	0.66 [0.43, 1.01]
SCO100470 2006	89/518	108/532	5.0 %	0.81 [0.60, 1.11]
Tashkin 2012a%b	88/880	69/444	4.2 %	0.60 [0.43, 0.85]
Subtotal (95% CI)	**3562**	**3127**	**37.5 %**	**0.83 [0.70, 0.98]**
Total events: 1382 (LABA/ICS), 1420 (LABA)				
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.15$, df = 5 (P = 0.15); $I^2 = 39\%$				
Test for overall effect: Z = 2.18 (P = 0.029)				
Total (95% CI)	**8268**	**7462**	**100.0 %**	**0.83 [0.77, 0.89]**
Total events: 3208 (LABA/ICS), 3283 (LABA)				



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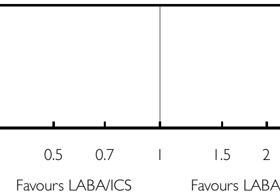
Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.0; Chi^2 = 14.48, df = 15 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 5.35 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.85), I^2 =0.0%					



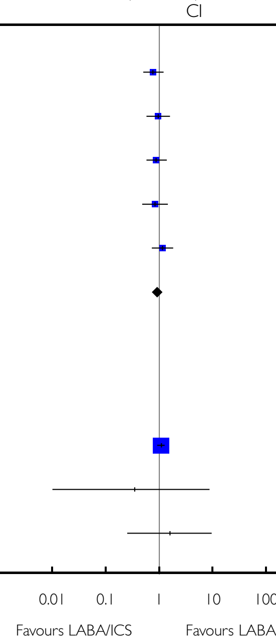
Analysis 5.2. Comparison 5 LABA/ICS vs LABA, Outcome 2 Severe exacerbations.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 2 Severe exacerbations

Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Anzueto 2009	39/385	50/393		8.2 %	0.77 [0.50, 1.21]
Calverley 2003 TRISTAN	32/358	35/372		6.4 %	0.95 [0.57, 1.56]
Ferguson 2008	42/391	46/385		8.2 %	0.89 [0.57, 1.38]
Fukuchi 2013	24/636	30/657		5.4 %	0.82 [0.47, 1.42]
Ohar 2014	43/314	39/325		7.5 %	1.16 [0.73, 1.85]
Subtotal (95% CI)	**2084**	**2132**		**35.6 %**	**0.91 [0.74, 1.13]**
Total events: 180 (LABA/ICS), 200 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.77, df = 4 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 0.87 (P = 0.38)					
2 Low-risk					
Calverley 2007	400/1533	373/1521		60.7 %	1.09 [0.92, 1.28]
Hanania 2003	0/118	1/124		0.2 %	0.35 [0.01, 8.61]
Mahler 2002	3/114	2/117		0.5 %	1.55 [0.25, 9.48]



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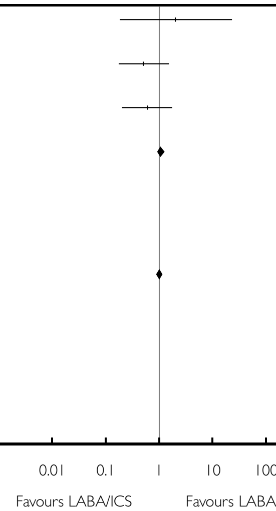
Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Rossi 2014	2/288	1/293		0.3 %	2.04 [0.18, 22.64]
SCO100470 2006	5/518	10/532		1.4 %	0.51 [0.17, 1.50]
Tashkin 2012a%b	7/880	6/444		1.3 %	0.59 [0.20, 1.75]
Subtotal (95% CI)	**3451**	**3031**		**64.4 %**	**1.06 [0.90, 1.24]**
Total events: 417 (LABA/ICS), 393 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.91, df = 5 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 0.70 (P = 0.48)					
Total (95% CI)	**5535**	**5163**		**100.0 %**	**1.00 [0.88, 1.14]**
Total events: 597 (LABA/ICS), 593 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 6.93, df = 10 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 0.04 (P = 0.97)					
Test for subgroup differences: Chi^2 = 1.25, df = 1 (P = 0.26), I^2 =20%					



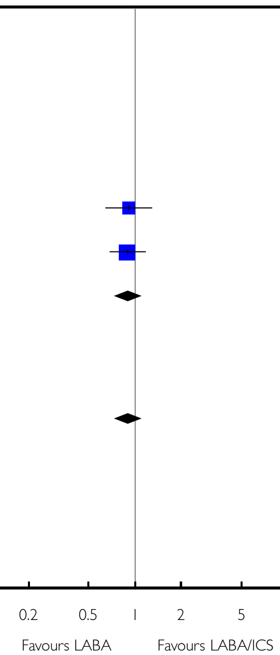
Analysis 5.3. Comparison 5 LABA/ICS vs LABA, Outcome 3 SGRQ responders at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 3 SGRQ responders at 3 months

Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA/ICS), 0 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low-risk					
Rossi 2014	109/257	114/255		36.8 %	0.91 [0.64, 1.29]
SCO100470 2006	272/452	291/463		63.2 %	0.89 [0.68, 1.17]
Subtotal (95% CI)	**709**	**718**		**100.0 %**	**0.90 [0.73, 1.11]**
Total events: 381 (LABA/ICS), 405 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.98 (P = 0.33)					
Total (95% CI)	**709**	**718**		**100.0 %**	**0.90 [0.73, 1.11]**
Total events: 381 (LABA/ICS), 405 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.98 (P = 0.33)					
Test for subgroup differences: Not applicable					



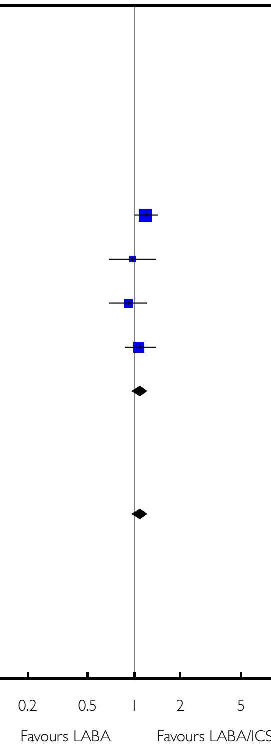
Analysis 5.4. Comparison 5 LABA/ICS vs LABA, Outcome 4 SGRQ responders at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 4 SGRQ responders at 6 months

Study or subgroup	LABA/ICS n/N	LABA n/N	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk				
Subtotal (95% CI)	**0**	**0**		**Not estimable**
Total events: 0 (LABA/ICS), 0 (LABA)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
2 Low-risk				
Calverley 2007	417/1009	379/1021	44.9 %	1.19 [1.00, 1.43]
Rossi 2014	118/242	118/238	11.1 %	0.97 [0.68, 1.38]
SCO100470 2006	266/413	281/422	17.5 %	0.91 [0.68, 1.21]
Tashkin 2012a%b	441/841	218/432	26.5 %	1.08 [0.86, 1.37]
Subtotal (95% CI)	**2505**	**2113**	**100.0 %**	**1.08 [0.96, 1.22]**
Total events: 1242 (LABA/ICS), 996 (LABA)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.98, df = 3 (P = 0.40); I^2 =0.0%				
Test for overall effect: Z = 1.31 (P = 0.19)				
Total (95% CI)	**2505**	**2113**	**100.0 %**	**1.08 [0.96, 1.22]**
Total events: 1242 (LABA/ICS), 996 (LABA)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.98, df = 3 (P = 0.40); I^2 =0.0%				
Test for overall effect: Z = 1.31 (P = 0.19)				
Test for subgroup differences: Not applicable				



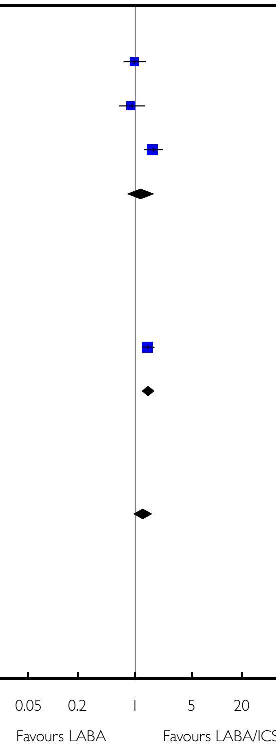
Analysis 5.5. Comparison 5 LABA/ICS vs LABA, Outcome 5 SGRQ responders at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 5 SGRQ responders at 12 months

Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Calverley 2003 TRISTAN	147/320	149/320		23.4 %	0.98 [0.71, 1.33]
Calverley 2010	111/470	59/233		20.8 %	0.91 [0.63, 1.31]
Kardos 2007	211/507	146/487		25.8 %	1.66 [1.28, 2.16]
Subtotal (95% CI)	**1297**	**1040**		**70.0 %**	**1.15 [0.78, 1.72]**
Total events: 469 (LABA/ICS), 354 (LABA)					
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 9.85$, df = 2 (P = 0.01); I^2 =80%					
Test for overall effect: Z = 0.71 (P = 0.48)					
2 Low-risk					
Calverley 2007	424/993	351/1019		30.0 %	1.42 [1.18, 1.70]
Subtotal (95% CI)	**993**	**1019**		**30.0 %**	**1.42 [1.18, 1.70]**
Total events: 424 (LABA/ICS), 351 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.80 (P = 0.00015)					
Total (95% CI)	**2290**	**2059**		**100.0 %**	**1.24 [0.95, 1.60]**
Total events: 893 (LABA/ICS), 705 (LABA)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 11.22$, df = 3 (P = 0.01); I^2 =73%					
Test for overall effect: Z = 1.59 (P = 0.11)					
Test for subgroup differences: $Chi^2 = 0.85$, df = 1 (P = 0.36), I^2 =0.0%					



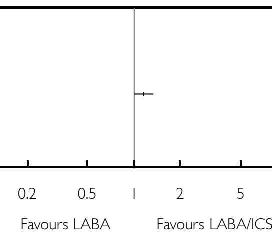
Analysis 5.6. Comparison 5 LABA/ICS vs LABA, Outcome 6 SGRQ responders at 3 years.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 6 SGRQ responders at 3 years

Study or subgroup	LABA/ICS n/N	LABA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 High-risk				
2 Low-risk				
Calverley 2007	275/932	252/984		1.15 [1.00, 1.33]



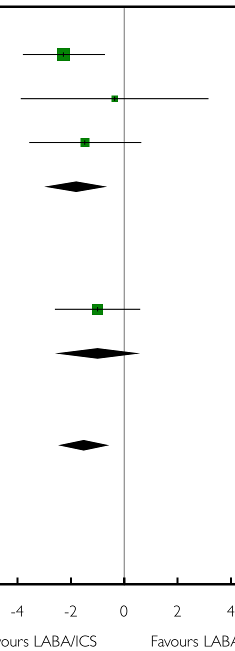
Analysis 5.7. Comparison 5 LABA/ICS vs LABA, Outcome 7 Change from baseline in SGRQ at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 7 Change from baseline in SGRQ at 3 months

Study or subgroup	LABA/ICS N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Anzueto 2009	314	-0.04 (9.87)	289	2.24 (9.47)		37.7 %	-2.28 [-3.82, -0.74]
Ferguson 2008	343	-0.38 (23.61)	313	-0.02 (22.4)		7.2 %	-0.36 [-3.88, 3.16]
Fukuchi 2013	636	-4.37 (19.1)	657	-2.9 (19.4)		20.4 %	-1.47 [-3.57, 0.63]
Subtotal (95% CI)	**1293**		**1259**			**65.3 %**	**-1.81 [-2.99, -0.64]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.11$, df = 2 (P = 0.57); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.03 (P = 0.0024)							
2 Low-risk							
SCO100470 2006	518	-8.8 (13.2)	532	-7.8 (13.38)		34.7 %	-1.00 [-2.61, 0.61]
Subtotal (95% CI)	**518**		**532**			**34.7 %**	**-1.00 [-2.61, 0.61]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.22 (P = 0.22)							
Total (95% CI)	**1811**		**1791**			**100.0 %**	**-1.53 [-2.48, -0.58]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.75$, df = 3 (P = 0.63); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.17 (P = 0.0015)							
Test for subgroup differences: $Chi^2 = 0.64$, df = 1 (P = 0.42), $I^2 = 0.0\%$							



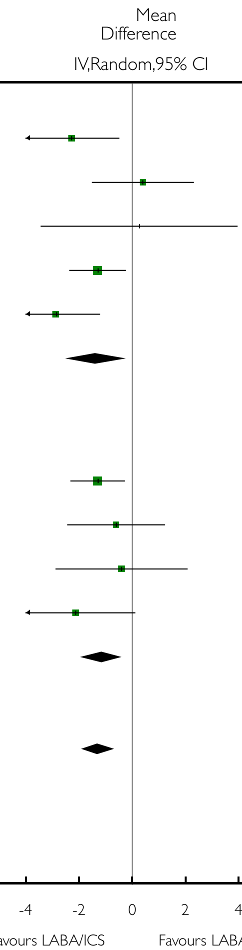
Analysis 5.8. Comparison 5 LABA/ICS vs LABA, Outcome 8 Change from baseline in SGRQ at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 8 Change from baseline in SGRQ at 6 months

Study or subgroup	LABA/ICS N	LABA/ICS Mean(SD)	LABA N	LABA Mean(SD)	Weight	Mean Difference IV,Random,95% CI
1 High-risk						
Anzueto 2009	285	-0.83 (11.09)	259	1.46 (10.57)	9.8 %	-2.29 [-4.11, -0.47]
Calverley 2003 TRISTAN	271	-3.4 (11.9)	268	-3.8 (10.8)	8.9 %	0.40 [-1.52, 2.32]
Ferguson 2008	309	0.09 (23.34)	271	-0.18 (22.09)	2.7 %	0.27 [-3.43, 3.97]
Ferguson 2017	589	-0.855 (8.941)	593	0.44 (9.452)	22.3 %	-1.30 [-2.35, -0.25]
Tashkin 2008	558	-4.1 (12.04)	284	-1.24 (11.35)	11.4 %	-2.86 [-4.52, -1.20]
Subtotal (95% CI)	**2012**		**1675**		**55.0 %**	**-1.40 [-2.53, -0.26]**
Heterogeneity: Tau^2 = 0.80; Chi^2 = 8.09, df = 4 (P = 0.09); I^2 =51%						
Test for overall effect: Z = 2.42 (P = 0.016)						
2 Low-risk						
Calverley 2007	941	-3.4 (11.35)	906	-2.1 (11.14)	22.9 %	-1.30 [-2.33, -0.27]
SCO100470 2006	518	-10.3 (15.25)	532	-9.7 (15.22)	9.6 %	-0.60 [-2.44, 1.24]
Tashkin 2012a	403	-6.58 (14.74)	201	-6.18 (14.72)	5.6 %	-0.40 [-2.89, 2.09]
Tashkin 2012b	438	-7.05 (13.98)	231	-4.93 (13.95)	6.9 %	-2.12 [-4.34, 0.10]
Subtotal (95% CI)	**2300**		**1870**		**45.0 %**	**-1.18 [-1.97, -0.40]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.49, df = 3 (P = 0.68); I^2 =0.0%						
Test for overall effect: Z = 2.94 (P = 0.0032)						
Total (95% CI)	**4312**		**3545**		**100.0 %**	**-1.32 [-1.94, -0.70]**
Heterogeneity: Tau^2 = 0.16; Chi^2 = 9.82, df = 8 (P = 0.28); I^2 =19%						
Test for overall effect: Z = 4.17 (P = 0.000030)						
Test for subgroup differences: Chi^2 = 0.09, df = 1 (P = 0.76), I^2 =0.0%						



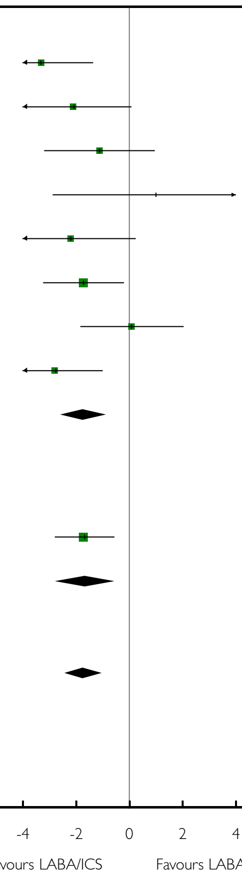
Analysis 5.9. Comparison 5 LABA/ICS vs LABA, Outcome 9 Change from baseline in SGRQ at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 9 Change from baseline in SGRQ at 12 months

Study or subgroup	LABA/ICS N	LABA/ICS Mean(SD)	LABA N	LABA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Anzueto 2009	251	-1.16 (11.14)	237	2.17 (10.82)		10.4 %	-3.33 [-5.28, -1.38]
Calverley 2003 TRISTAN	237	-4.5 (12.9)	224	-2.4 (10.9)		8.6 %	-2.10 [-4.28, 0.08]
Calverley 2010	470	-4.02 (12.94)	233	-2.9 (13.28)		9.4 %	-1.12 [-3.19, 0.95]
Ferguson 2008	268	0.09 (22.48)	268	-0.9 (23.28)		3.0 %	0.99 [-2.88, 4.86]
Kardos 2007	408	-2.9 (17.8)	384	-0.7 (17.2)		7.1 %	-2.20 [-4.64, 0.24]
Rennard 2009	895	-4.61 (13.62)	446	-2.9 (13.3)		15.4 %	-1.71 [-3.23, -0.19]
Sharafkhaneh 2012	741	-5.62 (15.43)	357	-5.71 (15.31)		10.5 %	0.09 [-1.85, 2.03]
Wedzicha 2014	595	-3.55 (15.61)	591	-0.77 (15.39)		12.2 %	-2.78 [-4.54, -1.02]
Subtotal (95% CI)	**3865**		**2740**			**76.7 %**	**-1.75 [-2.61, -0.89]**
Heterogeneity: Tau^2 = 0.44; Chi^2 = 9.80, df = 7 (P = 0.20); I^2 =29%							
Test for overall effect: Z = 3.97 (P = 0.000071)							
2 Low-risk							
Calverley 2007	873	-3.7 (11.82)	844	-2 (11.91)		23.3 %	-1.70 [-2.82, -0.58]
Subtotal (95% CI)	**873**		**844**			**23.3 %**	**-1.70 [-2.82, -0.58]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.97 (P = 0.0030)							
Total (95% CI)	**4738**		**3584**			**100.0 %**	**-1.75 [-2.44, -1.06]**
Heterogeneity: Tau^2 = 0.20; Chi^2 = 9.81, df = 8 (P = 0.28); I^2 =18%							
Test for overall effect: Z = 4.97 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.95), I^2 =0.0%							



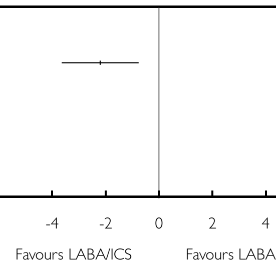
Analysis 5.10. Comparison 5 LABA/ICS vs LABA, Outcome 10 Change from baseline in SGRQ at 3 years.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 10 Change from baseline in SGRQ at 3 years

Study or subgroup	LABA/ICS N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 High-risk						
Calverley 2007	681	-1.2 (13.31)	634	1 (13.09)		-2.20 [-3.63, -0.77]
2 Low-risk						



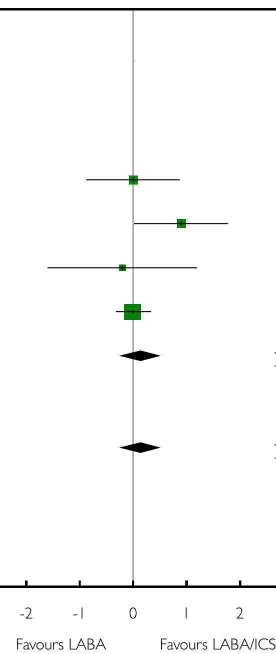
Analysis 5.11. Comparison 5 LABA/ICS vs LABA, Outcome 11 TDI at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 11 TDI at 3 months

Study or subgroup	LABA/ICS N	LABA/ICS Mean(SD)	LABA N	LABA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Hanania 2003	94	1.5 (3.23)	93	1.5 (2.91)		16.4 %	0.0 [-0.88, 0.88]
Mahler 2002	87	1.9 (3.22)	92	1 (2.78)		16.4 %	0.90 [0.02, 1.78]
Rossi 2014	288	1.69 (8.64)	293	1.89 (8.54)		7.2 %	-0.20 [-1.60, 1.20]
SCO100470 2006	505	1.9 (2.697)	516	1.9 (2.726)		60.0 %	0.0 [-0.33, 0.33]
Subtotal (95% CI)	**974**		**994**			**100.0 %**	**0.13 [-0.26, 0.52]**
Heterogeneity: Tau² = 0.04; Chi² = 3.72, df = 3 (P = 0.29); I² =19%							
Test for overall effect: Z = 0.67 (P = 0.50)							
Total (95% CI)	**974**		**994**			**100.0 %**	**0.13 [-0.26, 0.52]**
Heterogeneity: Tau² = 0.04; Chi² = 3.72, df = 3 (P = 0.29); I² =19%							
Test for overall effect: Z = 0.67 (P = 0.50)							
Test for subgroup differences: Not applicable							



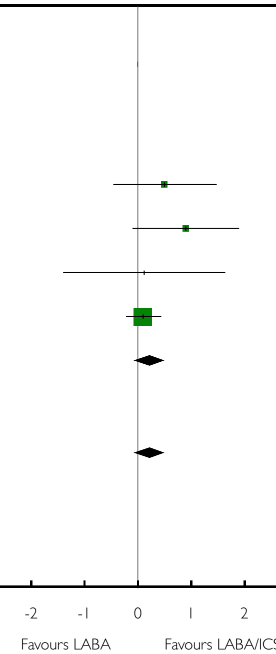
Analysis 5.12. Comparison 5 LABA/ICS vs LABA, Outcome 12 TDI at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 12 TDI at 6 months

Study or subgroup	LABA/ICS N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Hanania 2003	81	2.3 (3.03)	84	1.8 (3.31)		9.2 %	0.50 [-0.47, 1.47]
Mahler 2002	71	2.3 (3.15)	79	1.4 (3.06)		8.7 %	0.90 [-0.10, 1.90]
Rossi 2014	288	2.7 (9.37)	293	2.58 (9.29)		3.8 %	0.12 [-1.40, 1.64]
SCO100470 2006	505	2.5 (2.697)	516	2.4 (2.726)		78.3 %	0.10 [-0.23, 0.43]
Subtotal (95% CI)	**945**		**972**			**100.0 %**	**0.21 [-0.09, 0.50]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.62$, df = 3 (P = 0.45); I^2 =0.0%							
Test for overall effect: Z = 1.38 (P = 0.17)							
Total (95% CI)	**945**		**972**			**100.0 %**	**0.21 [-0.09, 0.50]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.62$, df = 3 (P = 0.45); I^2 =0.0%							
Test for overall effect: Z = 1.38 (P = 0.17)							
Test for subgroup differences: Not applicable							



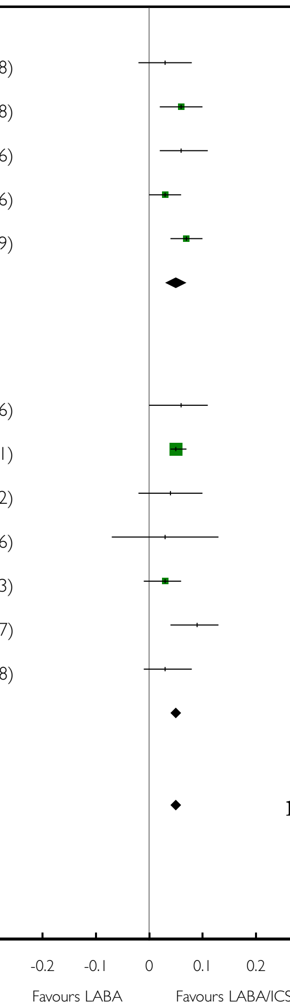
Analysis 5.13. Comparison 5 LABA/ICS vs LABA, Outcome 13 Change from baseline in FEV1 at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 13 Change from baseline in FEV1 at 3 months

Study or subgroup	LABA/ICS N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Anzueto 2009	340	-0.021 (0.313)	314	-0.05 (0.338)		3.4 %	0.03 [-0.02, 0.08]
Calverley 2003 TRISTAN	309	0.134 (0.264)	326	0.08 (0.258)		5.1 %	0.06 [0.02, 0.10]
Ferguson 2008	352	0.022 (0.326)	315	-0.04 (0.286)		3.9 %	0.06 [0.02, 0.11]
Fukuchi 2013	636	0.044 (0.252)	657	0.01 (0.256)		11.0 %	0.03 [0.00, 0.06]
Wedzicha 2014	595	0.081 (0.244)	591	0.01 (0.219)		12.1 %	0.07 [0.04, 0.10]
Subtotal (95% CI)	**2232**		**2203**			**35.5 %**	**0.05 [0.03, 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 5.29, df = 4 (P = 0.26); I² =24%							
Test for overall effect: Z = 5.40 (P < 0.00001)							
2 Low-risk							
Hanania 2003	144	0.166 (0.246)	135	0.11 (0.216)		2.9 %	0.06 [0.00, 0.11]
Hoshino 2013	16	0.115 (0.018)	14	0.06 (0.021)		42.4 %	0.05 [0.04, 0.07]
Mahler 2002	86	0.137 (0.179)	91	0.1 (0.222)		2.4 %	0.04 [-0.02, 0.10]
Rossi 2014	288	0.074 (0.628)	293	0.04 (0.616)		0.8 %	0.03 [-0.07, 0.13]
SCO100470 2006	508	0.074 (0.27)	517	0.05 (0.273)		7.6 %	0.03 [-0.01, 0.06]
Tashkin 2012a	416	0.085 (0.271)	208	0 (0.27)		4.2 %	0.09 [0.04, 0.13]
Tashkin 2012b	443	0.08 (0.281)	235	0.05 (0.28)		4.3 %	0.03 [-0.01, 0.08]
Subtotal (95% CI)	**1901**		**1493**			**64.5 %**	**0.05 [0.04, 0.06]**
Heterogeneity: Tau² = 0.0; Chi² = 5.35, df = 6 (P = 0.50); I² =0.0%							
Test for overall effect: Z = 8.59 (P < 0.00001)							
Total (95% CI)	**4133**		**3696**			**100.0 %**	**0.05 [0.04, 0.06]**
Heterogeneity: Tau² = 0.0; Chi² = 10.64, df = 11 (P = 0.47); I² =0.0%							
Test for overall effect: Z = 10.75 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² =0.0%							



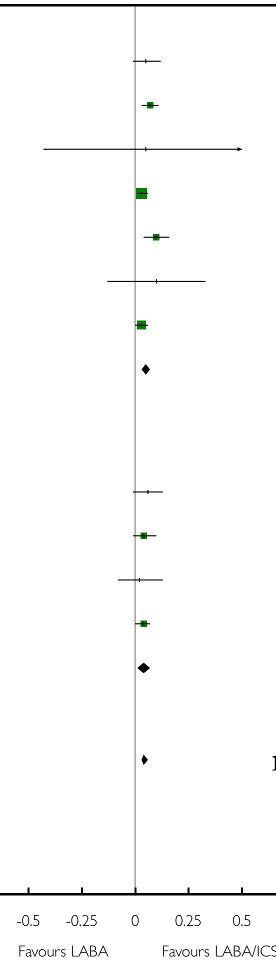
Analysis 5.14. Comparison 5 LABA/ICS vs LABA, Outcome 14 Change from baseline in FEV1 at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 14 Change from baseline in FEV1 at 6 months

Study or subgroup	LABA/ICS N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Anzueto 2009	306	0.001 (0.427)	275	-0.05 (0.353)		4.3 %	0.05 [-0.01, 0.12]
Calverley 2003 TRISTAN	298	0.122 (0.287)	310	0.05 (0.24)		9.8 %	0.07 [0.03, 0.11]
Ferguson 2008	321	-0.012 (3.297)	277	-0.06 (2.713)		0.1 %	0.05 [-0.43, 0.53]
Ferguson 2017	606	0.008 (0.21)	613	-0.03 (0.198)		33.1 %	0.03 [0.01, 0.06]
Ohar 2014	280	0.14 (0.351)	271	0.04 (0.313)		5.6 %	0.10 [0.04, 0.16]
SCO40041 2008	80	0.148 (0.769)	81	0.05 (0.738)		0.3 %	0.10 [-0.13, 0.33]
Tashkin 2008	558	0.08 (0.206)	284	0.05 (0.19)		22.3 %	0.03 [0.00, 0.06]
Subtotal (95% CI)	**2449**		**2111**			**75.5 %**	**0.05 [0.03, 0.07]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.55$, df = 6 (P = 0.27); I^2 =21%							
Test for overall effect: Z = 4.81 (P < 0.00001)							
2 Low-risk							
Hanania 2003	124	0.165 (0.289)	119	0.1 (0.259)		3.7 %	0.06 [-0.01, 0.13]
Mahler 2002	70	0.133 (0.133)	76	0.09 (0.197)		5.9 %	0.04 [-0.01, 0.10]
Rossi 2014	288	0.039 (0.662)	293	0.02 (0.65)		1.5 %	0.02 [-0.08, 0.13]
SCO100470 2006	508	0.06 (0.293)	517	0.02 (0.296)		13.4 %	0.04 [0.00, 0.07]
Subtotal (95% CI)	**990**		**1005**			**24.5 %**	**0.04 [0.01, 0.07]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.60$, df = 3 (P = 0.90); I^2 =0.0%							
Test for overall effect: Z = 3.02 (P = 0.0025)							
Total (95% CI)	**3439**		**3116**			**100.0 %**	**0.04 [0.03, 0.06]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.18$, df = 10 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 6.37 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.14$, df = 1 (P = 0.71), I^2 =0.0%							



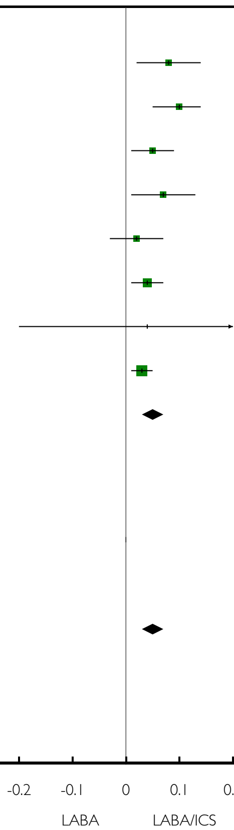
Analysis 5.15. Comparison 5 LABA/ICS vs LABA, Outcome 15 Change from baseline in FEV1 at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 15 Change from baseline in FEV1 at 12 months

Study or subgroup	LABA/ICS N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Anzueto 2009	269	-0.017 (0.349)	246	-0.1 (0.334)		7.8 %	0.08 [0.02, 0.14]
Calverley 2003 TRISTAN	269	0.113 (0.286)	255	0.02 (0.255)		11.3 %	0.10 [0.05, 0.14]
Calverley 2010	470	0.08 (0.28)	233	0.03 (0.28)		12.2 %	0.05 [0.01, 0.09]
Ferguson 2008	276	-0.012 (0.375)	235	-0.08 (0.261)		8.6 %	0.07 [0.01, 0.13]
Kardos 2007	408	0.07 (0.343)	384	0.05 (0.333)		11.0 %	0.02 [-0.03, 0.07]
Rennard 2009	121	0.1 (0.11)	124	0.06 (0.11)		21.4 %	0.04 [0.01, 0.07]
SCO40041 2008	73	0.095 (0.769)	68	0.05 (0.734)		0.5 %	0.05 [-0.20, 0.29]
Sharafkhaneh 2012	798	0.07 (0.175)	399	0.04 (0.17)		27.3 %	0.03 [0.01, 0.05]
Subtotal (95% CI)	**2684**		**1944**			**100.0 %**	**0.05 [0.03, 0.07]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 10.41$, df = 7 (P = 0.17); $I^2 = 33\%$							
Test for overall effect: Z = 5.22 (P < 0.00001)							
2 Low-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**2684**		**1944**			**100.0 %**	**0.05 [0.03, 0.07]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 10.41$, df = 7 (P = 0.17); $I^2 = 33\%$							
Test for overall effect: Z = 5.22 (P < 0.00001)							
Test for subgroup differences: Not applicable							



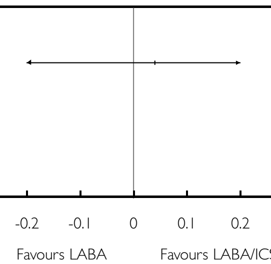
Analysis 5.16. Comparison 5 LABA/ICS vs LABA, Outcome 16 Change from baseline in FEV1 at 3 years.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 16 Change from baseline in FEV1 at 3 years

Study or subgroup	LABA/ICS		LABA		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
1 High-risk						
SCO40041 2008	56	0.111 (0.681)	55	0.08 (0.779)		0.04 [-0.24, 0.31]
2 Low-risk						



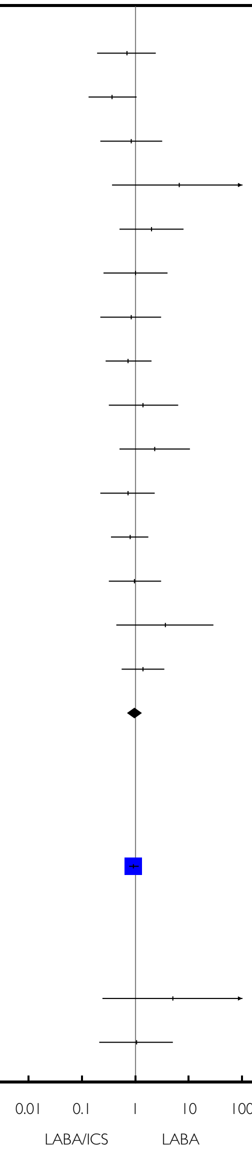
Analysis 5.17. Comparison 5 LABA/ICS vs LABA, Outcome 17 Mortality.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 17 Mortality

Study or subgroup	LABA/ICS n/N	LABA n/N	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk				
Anzueto 2009	4/385	6/393	1.9 %	0.68 [0.19, 2.42]
Calverley 2003	5/254	13/255	2.7 %	0.37 [0.13, 1.06]
Calverley 2003 TRISTAN	4/358	5/372	1.7 %	0.83 [0.22, 3.11]
Calverley 2010	6/470	0/233	0.4 %	6.53 [0.37, 116.50]
Ferguson 2008	6/391	3/385	1.5 %	1.98 [0.49, 7.99]
Ferguson 2017	4/606	4/613	1.6 %	1.01 [0.25, 4.06]
Fukuchi 2013	4/636	5/657	1.7 %	0.83 [0.22, 3.09]
Kardos 2007	7/507	9/487	3.0 %	0.74 [0.27, 2.01]
Ohar 2014	4/314	3/325	1.3 %	1.38 [0.31, 6.24]
Rennard 2009	9/989	2/494	1.3 %	2.26 [0.49, 10.50]
SCO40041 2008	5/92	7/94	2.1 %	0.71 [0.22, 2.34]
Sharafkhaneh 2012	16/815	10/403	4.7 %	0.79 [0.35, 1.75]
Szafranski 2003	6/208	6/201	2.3 %	0.97 [0.31, 3.04]
Tashkin 2008	7/558	1/284	0.7 %	3.60 [0.44, 29.37]
Wedzicha 2014	11/601	8/596	3.6 %	1.37 [0.55, 3.43]
Subtotal (95% CI)	**7184**	**5792**	**30.5 %**	**0.95 [0.69, 1.30]**
Total events: 98 (LABA/ICS), 82 (LABA)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 10.56, df = 14 (P = 0.72); I^2 =0.0%				
Test for overall effect: Z = 0.34 (P = 0.73)				
2 Low-risk				
Calverley 2007	193/1533	205/1521	67.6 %	0.92 [0.75, 1.14]
Hanania 2003	0/178	0/177		Not estimable
Mahler 2002	0/165	0/160		Not estimable
Rossi 2014	2/288	0/293	0.3 %	5.12 [0.24, 107.16]
SCO100470 2006	3/518	3/532	1.2 %	1.03 [0.21, 5.11]



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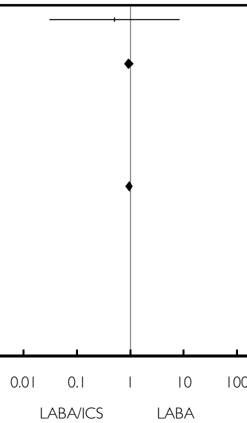
Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Tashkin 2012a%b	1/888	1/452		0.4 %	0.51 [0.03, 8.15]
Subtotal (95% CI)	**3570**	**3135**		**69.5 %**	**0.93 [0.76, 1.15]**
Total events: 199 (LABA/ICS), 209 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.41, df = 3 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 0.68 (P = 0.50)					
Total (95% CI)	**10754**	**8927**		**100.0 %**	**0.94 [0.79, 1.11]**
Total events: 297 (LABA/ICS), 291 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 11.95, df = 18 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 0.76 (P = 0.45)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.93), I^2 =0.0%					



Analysis 5.18. Comparison 5 LABA/ICS vs LABA, Outcome 18 Total SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 18 Total SAE

Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Anzueto 2009	82/394	71/403		5.8 %	1.23 [0.86, 1.75]
Calverley 2003 TRISTAN	62/358	69/372		5.1 %	0.92 [0.63, 1.34]
Calverley 2010	43/478	14/238		2.1 %	1.58 [0.85, 2.95]
Ferguson 2008	91/391	81/385		6.1 %	1.14 [0.81, 1.60]
Ferguson 2017	49/606	63/613		4.9 %	0.77 [0.52, 1.14]
Fukuchi 2013	43/636	45/657		4.1 %	0.99 [0.64, 1.52]
Kardos 2007	76/507	88/487		6.2 %	0.80 [0.57, 1.12]
Ohar 2014	75/314	82/325		5.6 %	0.93 [0.65, 1.33]
Rennard 2009	148/989	89/494		7.9 %	0.80 [0.60, 1.07]
SCO40041 2008	33/92	36/94		2.3 %	0.90 [0.50, 1.63]
Sharafkhaneh 2012	140/815	74/403		7.0 %	0.92 [0.68, 1.26]
Szafranski 2003	43/208	37/201		3.3 %	1.16 [0.71, 1.89]
Tashkin 2008	61/558	23/284		3.1 %	1.39 [0.84, 2.30]
Wedzicha 2014	106/601	94/596		7.3 %	1.14 [0.84, 1.55]
Subtotal (95% CI)	**6947**	**5552**		**70.9 %**	**0.99 [0.89, 1.09]**
Total events: 1052 (LABA/ICS), 866 (LABA)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 13.07$, df = 13 (P = 0.44); $I^2 = 1\%$					
Test for overall effect: Z = 0.27 (P = 0.78)					
2 Low-risk					
Calverley 2007	665/1533	617/1521		18.0 %	1.12 [0.97, 1.30]
Hanania 2003	8/178	5/177		0.7 %	1.62 [0.52, 5.05]
Mahler 2002	9/165	7/160		0.8 %	1.26 [0.46, 3.47]
Rossi 2014	17/288	5/293		0.8 %	3.61 [1.31, 9.93]
SCO100470 2006	35/518	29/532		3.1 %	1.26 [0.76, 2.09]
Tashkin 2012a%b	96/888	54/452		5.7 %	0.89 [0.63, 1.27]

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Favours LABA/ICS Favours LABA

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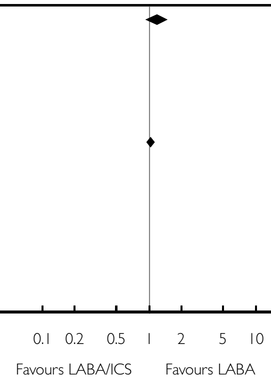
Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Subtotal (95% CI)	**3570**	**3135**		**29.1 %**	**1.17 [0.92, 1.47]**
Total events: 830 (LABA/ICS), 717 (LABA)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 7.38$, df = 5 (P = 0.19); I^2 =32%					
Test for overall effect: Z = 1.29 (P = 0.20)					
Total (95% CI)	**10517**	**8687**		**100.0 %**	**1.03 [0.94, 1.13]**
Total events: 1882 (LABA/ICS), 1583 (LABA)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 23.04$, df = 19 (P = 0.24); I^2 =18%					
Test for overall effect: Z = 0.63 (P = 0.53)					
Test for subgroup differences: $Chi^2 = 1.68$, df = 1 (P = 0.20), I^2 =40%					



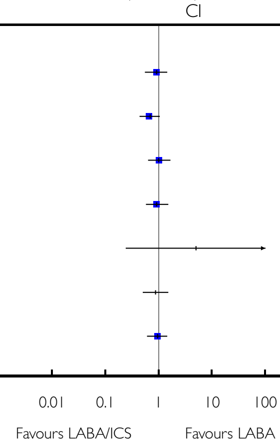
Analysis 5.19. Comparison 5 LABA/ICS vs LABA, Outcome 19 COPD SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 19 COPD SAE

Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Anzueto 2009	34/394	38/403		5.5 %	0.91 [0.56, 1.47]
Calverley 2003	40/254	55/255		6.3 %	0.68 [0.43, 1.07]
Calverley 2003 TRISTAN	38/358	39/372		5.8 %	1.01 [0.63, 1.63]
Ferguson 2008	37/391	39/385		5.7 %	0.93 [0.58, 1.49]
Ferguson 2017	2/606	0/613		0.1 %	5.07 [0.24, 105.92]
Fukuchi 2013	24/636	28/657		4.2 %	0.88 [0.50, 1.54]
Ohar 2014	47/314	51/325		6.9 %	0.95 [0.61, 1.45]



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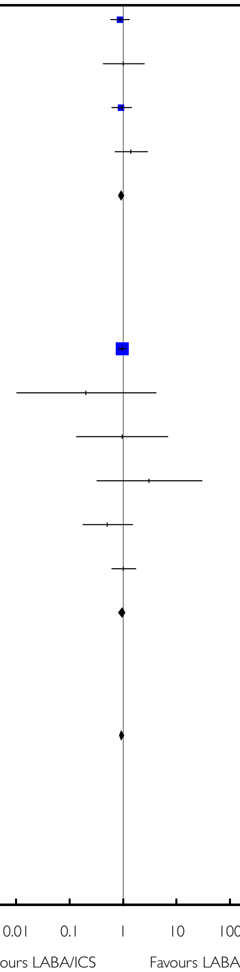
Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Rennard 2009	68/989	39/494		7.7 %	0.86 [0.57, 1.30]
SCO40041 2008	11/92	11/94		1.6 %	1.02 [0.42, 2.50]
Sharafkhaneh 2012	65/815	34/403		6.9 %	0.94 [0.61, 1.45]
Tashkin 2008	30/558	11/284		2.6 %	1.41 [0.70, 2.86]
Subtotal (95% CI)	**5407**	**4285**		**53.3 %**	**0.92 [0.78, 1.07]**
Total events: 396 (LABA/ICS), 345 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.72, df = 10 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 1.10 (P = 0.27)					
2 Low-risk					
Calverley 2007	298/1533	307/1521		40.6 %	0.95 [0.80, 1.14]
Hanania 2003	0/178	2/177		0.1 %	0.20 [0.01, 4.13]
Mahler 2002	2/165	2/160		0.3 %	0.97 [0.13, 6.97]
Rossi 2014	3/288	1/293		0.2 %	3.07 [0.32, 29.72]
SCO100470 2006	5/518	10/532		1.1 %	0.51 [0.17, 1.50]
Tashkin 2012a%b	40/888	20/452		4.3 %	1.02 [0.59, 1.76]
Subtotal (95% CI)	**3570**	**3135**		**46.7 %**	**0.95 [0.80, 1.12]**
Total events: 348 (LABA/ICS), 342 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.41, df = 5 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.52)					
Total (95% CI)	**8977**	**7420**		**100.0 %**	**0.93 [0.83, 1.04]**
Total events: 744 (LABA/ICS), 687 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 8.21, df = 16 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 1.24 (P = 0.21)					
Test for subgroup differences: Chi^2 = 0.08, df = 1 (P = 0.77), I^2 =0.0%					



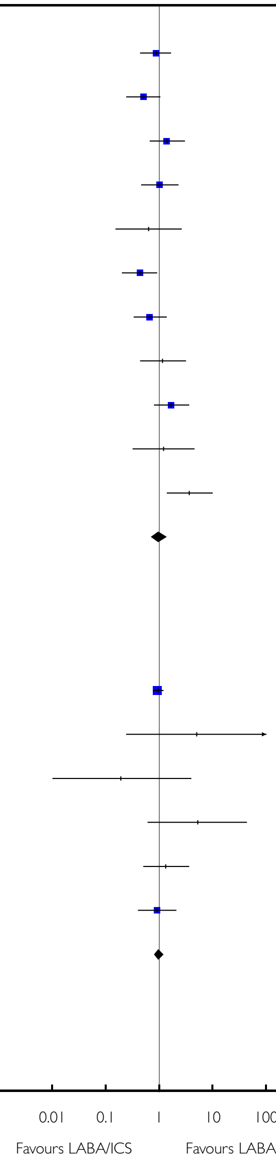
Analysis 5.20. Comparison 5 LABA/ICS vs LABA, Outcome 20 Cardiac SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 20 Cardiac SAE

Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Anzueto 2009	16/394	19/403		8.3 %	0.86 [0.43, 1.69]
Calverley 2003 TRISTAN	11/358	22/372		7.5 %	0.50 [0.24, 1.06]
Ferguson 2008	17/391	12/385		7.3 %	1.41 [0.67, 3.00]
Ferguson 2017	12/606	12/613		6.6 %	1.01 [0.45, 2.27]
Fukuchi 2013	3/636	5/657		2.7 %	0.62 [0.15, 2.60]
Ohar 2014	10/314	23/325		7.2 %	0.43 [0.20, 0.92]
Rennard 2009	19/989	14/494		8.1 %	0.67 [0.33, 1.35]
SCO40041 2008	9/92	8/94		4.9 %	1.17 [0.43, 3.17]
Sharafkhaneh 2012	30/815	9/403		7.3 %	1.67 [0.79, 3.56]
Tashkin 2008	7/558	3/284		2.9 %	1.19 [0.31, 4.64]
Wedzicha 2014	18/601	5/596		4.9 %	3.65 [1.35, 9.89]
Subtotal (95% CI)	**5754**	**4626**		**67.7 %**	**0.97 [0.68, 1.38]**
Total events: 152 (LABA/ICS), 132 (LABA)					
Heterogeneity: Tau^2 = 0.16; Chi^2 = 18.87, df = 10 (P = 0.04); I^2 =47%					
Test for overall effect: Z = 0.19 (P = 0.85)					
2 Low-risk					
Calverley 2007	160/1533	168/1521		18.3 %	0.94 [0.75, 1.18]
Hanania 2003	2/178	0/177		0.7 %	5.03 [0.24, 105.49]
Mahler 2002	0/165	2/160		0.7 %	0.19 [0.01, 4.02]
Rossi 2014	5/288	1/293		1.3 %	5.16 [0.60, 44.43]
SCO100470 2006	9/518	7/532		4.9 %	1.33 [0.49, 3.59]
Tashkin 2012a%b	16/888	9/452		6.5 %	0.90 [0.40, 2.06]
Subtotal (95% CI)	**3570**	**3135**		**32.3 %**	**0.97 [0.78, 1.21]**
Total events: 192 (LABA/ICS), 187 (LABA)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 5.02, df = 5 (P = 0.41); I^2 =0%					
Test for overall effect: Z = 0.28 (P = 0.78)					



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Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Total (95% CI)	**9324**	**7761**		**100.0 %**	**0.99 [0.77, 1.27]**
Total events: 344 (LABA/ICS), 319 (LABA)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 23.92, df = 16 (P = 0.09); I^2 =33%					
Test for overall effect: Z = 0.11 (P = 0.91)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.99), I^2 =0.0%					

0.01 0.1 1 10 100

Favours LABA/ICS Favours LABA

Analysis 5.21. Comparison 5 LABA/ICS vs LABA, Outcome 21 Dropouts due to adverse events.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 21 Dropouts due to adverse events

Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Anzueto 2009	37/394	39/403		4.5 %	0.97 [0.60, 1.55]
Calverley 2003	20/254	20/255		2.4 %	1.00 [0.53, 1.92]
Calverley 2003 TRISTAN	46/358	61/372		5.9 %	0.75 [0.50, 1.14]
Calverley 2010	15/478	5/238		1.0 %	1.51 [0.54, 4.20]
Ferguson 2008	26/391	33/385		3.5 %	0.76 [0.45, 1.30]
Ferguson 2017	3/606	5/613		0.5 %	0.60 [0.14, 2.54]
Fukuchi 2013	21/636	28/657		3.0 %	0.77 [0.43, 1.37]
Kardos 2007	61/507	61/487		7.0 %	0.96 [0.65, 1.40]
Ohar 2014	28/314	28/325		3.3 %	1.04 [0.60, 1.80]
Rennard 2009	117/989	60/494		9.1 %	0.97 [0.70, 1.35]

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Favours LABA/ICS Favours LABA

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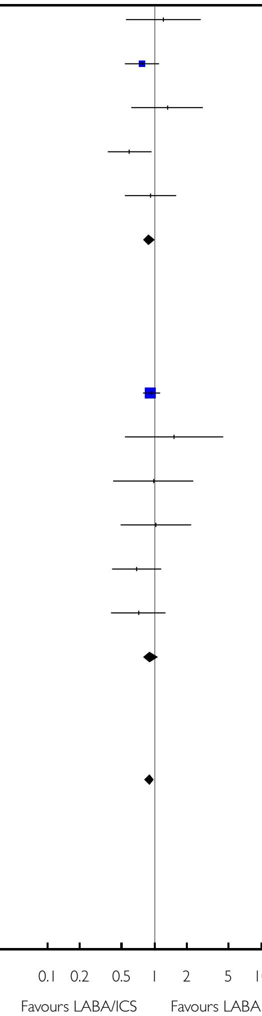
Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
SCO40041 2008	15/92	13/94		1.5 %	1.21 [0.54, 2.72]
Sharafkhaneh 2012	79/815	50/403		7.1 %	0.76 [0.52, 1.10]
Szafranski 2003	16/208	12/201		1.7 %	1.31 [0.60, 2.85]
Tashkin 2008	41/558	34/284		4.4 %	0.58 [0.36, 0.94]
Wedzicha 2014	26/601	28/596		3.4 %	0.92 [0.53, 1.58]
Subtotal (95% CI)	**7201**	**5807**		**58.2 %**	**0.88 [0.77, 1.00]**
Total events: 551 (LABA/ICS), 477 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 8.67, df = 14 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 1.99 (P = 0.047)					
2 Low-risk					
Calverley 2007	289/1533	303/1521		31.2 %	0.93 [0.78, 1.12]
Hanania 2003	9/178	6/177		0.9 %	1.52 [0.53, 4.36]
Mahler 2002	11/165	11/160		1.3 %	0.97 [0.41, 2.30]
Rossi 2014	14/288	14/293		1.7 %	1.02 [0.48, 2.18]
SCO100470 2006	25/518	37/532		3.7 %	0.68 [0.40, 1.14]
Tashkin 2012a%b	28/888	20/452		2.9 %	0.70 [0.39, 1.26]
Subtotal (95% CI)	**3570**	**3135**		**41.8 %**	**0.90 [0.77, 1.06]**
Total events: 376 (LABA/ICS), 391 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.04, df = 5 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 1.28 (P = 0.20)					
Total (95% CI)	**10771**	**8942**		**100.0 %**	**0.89 [0.80, 0.98]**
Total events: 927 (LABA/ICS), 868 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 11.80, df = 20 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 2.34 (P = 0.019)					
Test for subgroup differences: Chi^2 = 0.10, df = 1 (P = 0.76), I^2 =0.0%					



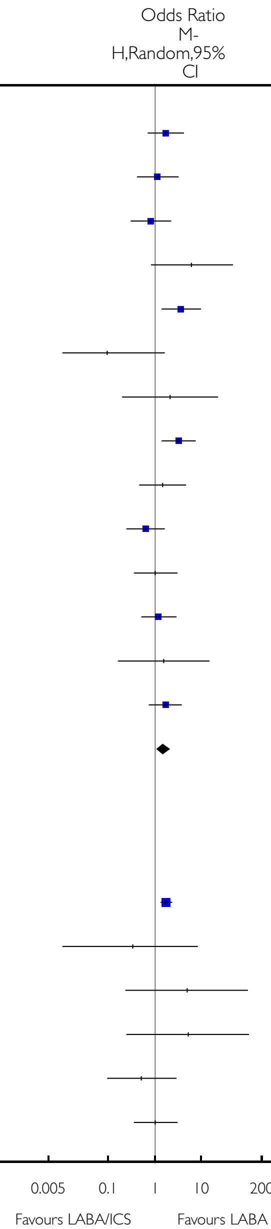
Analysis 5.22. Comparison 5 LABA/ICS vs LABA, Outcome 22 Pneumonia.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 5 LABA/ICS vs LABA

Outcome: 22 Pneumonia

Study or subgroup	LABA/ICS n/N	LABA n/N	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk				
Anzueto 2009	13/394	8/403	6.8 %	1.68 [0.69, 4.11]
Calverley 2003	8/254	7/255	5.4 %	1.15 [0.41, 3.23]
Calverley 2003 TRISTAN	7/358	9/372	5.7 %	0.80 [0.30, 2.18]
Calverley 2010	12/470	1/233	1.5 %	6.08 [0.79, 47.03]
Ferguson 2008	18/391	5/385	5.7 %	3.67 [1.35, 9.98]
Ferguson 2017	0/606	5/613	0.8 %	0.09 [0.01, 1.65]
Fukuchi 2013	2/636	1/657	1.1 %	2.07 [0.19, 22.88]
Kardos 2007	23/507	7/487	7.3 %	3.26 [1.39, 7.67]
Ohar 2014	7/314	5/325	4.4 %	1.46 [0.46, 4.65]
Rennard 2009	10/989	8/494	6.3 %	0.62 [0.24, 1.58]
SCO40041 2008	7/92	7/94	4.9 %	1.02 [0.34, 3.04]
Sharafkhaneh 2012	17/815	7/403	6.9 %	1.21 [0.50, 2.93]
Tashkin 2008	3/558	1/284	1.3 %	1.53 [0.16, 14.77]
Wedzicha 2014	15/601	9/596	7.6 %	1.67 [0.72, 3.85]
Subtotal (95% CI)	**6985**	**5601**	**65.8 %**	**1.46 [1.03, 2.08]**
Total events: 142 (LABA/ICS), 80 (LABA)				
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 17.69$, df = 13 (P = 0.17); I^2 =26%				
Test for overall effect: Z = 2.11 (P = 0.035)				
2 Low-risk				
Calverley 2007	138/1533	82/1521	25.0 %	1.74 [1.31, 2.30]
Hanania 2003	0/178	1/177	0.6 %	0.33 [0.01, 8.15]
Mahler 2002	2/165	0/160	0.7 %	4.91 [0.23, 103.04]
Rossi 2014	2/288	0/293	0.7 %	5.12 [0.24, 107.16]
SCO100470 2006	2/518	4/532	2.2 %	0.51 [0.09, 2.81]
Tashkin 2012a%b	10/888	5/452	5.0 %	1.02 [0.35, 3.00]



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Study or subgroup	LABA/ICS n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Subtotal (95% CI)	**3570**	**3135**		**34.2 %**	**1.64 [1.25, 2.14]**
Total events: 154 (LABA/ICS), 92 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.70, df = 5 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 3.62 (P = 0.00029)					
Total (95% CI)	**10555**	**8736**		**100.0 %**	**1.48 [1.14, 1.92]**
Total events: 296 (LABA/ICS), 172 (LABA)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 22.64, df = 19 (P = 0.25); I^2 =16%					
Test for overall effect: Z = 2.96 (P = 0.0030)					
Test for subgroup differences: Chi^2 = 0.25, df = 1 (P = 0.62), I^2 =0.0%					

0.005 0.1 1 10 200

Favours LABA/ICS Favours LABA

Analysis 6.1. Comparison 6 LAMA vs LABA, Outcome 1 Moderate to severe exacerbations.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 1 Moderate to severe exacerbations

Study or subgroup	LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Vogelmeier 2011	1277/3707	1414/3669		72.5 %	0.84 [0.76, 0.92]
Subtotal (95% CI)	**3707**	**3669**		**72.5 %**	**0.84 [0.76, 0.92]**
Total events: 1277 (LAMA), 1414 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.65 (P = 0.00026)					
2 Low-risk					
Bateman 2013	174/953	103/476		8.8 %	0.81 [0.62, 1.06]
Briggs 2005	30/328	36/325		2.5 %	0.81 [0.48, 1.35]
Brusasco 2003	129/402	142/405		7.6 %	0.88 [0.65, 1.17]

0.5 0.7 1 1.5 2

Favours LAMA Favours LABA

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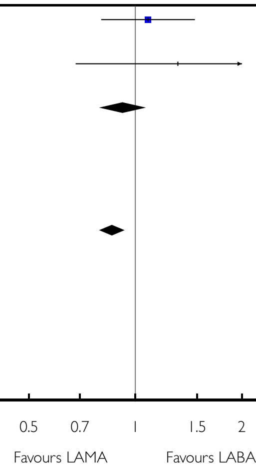
Study or subgroup	LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Donohue 2010	79/415	148/832		7.1 %	1.09 [0.80, 1.47]
Vogelmeier 2008	23/221	17/210		1.5 %	1.32 [0.68, 2.55]
Subtotal (95% CI)	**2319**	**2248**		**27.5 %**	**0.92 [0.79, 1.07]**
Total events: 435 (LAMA), 446 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.52, df = 4 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 1.11 (P = 0.27)					
Total (95% CI)	**6026**	**5917**		**100.0 %**	**0.86 [0.79, 0.93]**
Total events: 1712 (LAMA), 1860 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.47, df = 5 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.69 (P = 0.00023)					
Test for subgroup differences: Chi^2 = 0.94, df = 1 (P = 0.33), I^2 =0.0%					



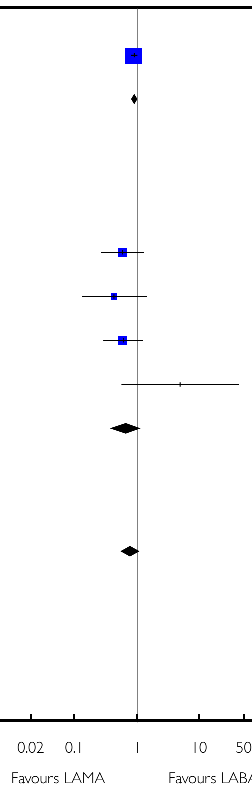
Analysis 6.2. Comparison 6 LAMA vs LABA, Outcome 2 Severe exacerbations.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 2 Severe exacerbations

Study or subgroup	LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Vogelmeier 2011	503/3707	553/3669		55.0 %	0.88 [0.78, 1.01]
Subtotal (95% CI)	**3707**	**3669**		**55.0 %**	**0.88 [0.78, 1.01]**
Total events: 503 (LAMA), 553 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.84 (P = 0.065)					
2 Low-risk					
Bateman 2013	14/953	12/476		16.2 %	0.58 [0.26, 1.26]
Briggs 2005	4/328	9/325		8.2 %	0.43 [0.13, 1.42]
Brusasco 2003	12/402	20/405		17.8 %	0.59 [0.29, 1.23]
Vogelmeier 2008	5/221	1/210		2.8 %	4.84 [0.56, 41.76]
Subtotal (95% CI)	**1904**	**1416**		**45.0 %**	**0.64 [0.36, 1.13]**
Total events: 35 (LAMA), 42 (LABA)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 3.93$, df = 3 (P = 0.27); I^2 =24%					
Test for overall effect: Z = 1.55 (P = 0.12)					
Total (95% CI)	**5611**	**5085**		**100.0 %**	**0.76 [0.53, 1.10]**
Total events: 538 (LAMA), 595 (LABA)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 5.94$, df = 4 (P = 0.20); I^2 =33%					
Test for overall effect: Z = 1.47 (P = 0.14)					
Test for subgroup differences: $Chi^2 = 1.21$, df = 1 (P = 0.27), I^2 =18%					



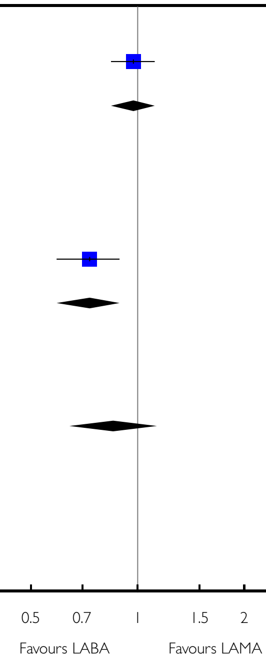
Analysis 6.3. Comparison 6 LAMA vs LABA, Outcome 3 SGRQ responders at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 3 SGRQ responders at 3 months

Study or subgroup	LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Decramer 2013	725/1503	732/1496		53.2 %	0.97 [0.84, 1.12]
Subtotal (95% CI)	**1503**	**1496**		**53.2 %**	**0.97 [0.84, 1.12]**
Total events: 725 (LAMA), 732 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.38 (P = 0.70)					
2 Low-risk					
Buhl 2011	320/753	375/743		46.8 %	0.73 [0.59, 0.89]
Subtotal (95% CI)	**753**	**743**		**46.8 %**	**0.73 [0.59, 0.89]**
Total events: 320 (LAMA), 375 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.09 (P = 0.0020)					
Total (95% CI)	**2256**	**2239**		**100.0 %**	**0.85 [0.64, 1.13]**
Total events: 1045 (LAMA), 1107 (LABA)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 5.33, df = 1 (P = 0.02); I^2 =81%					
Test for overall effect: Z = 1.13 (P = 0.26)					
Test for subgroup differences: Chi^2 = 5.33, df = 1 (P = 0.02), I^2 =81%					



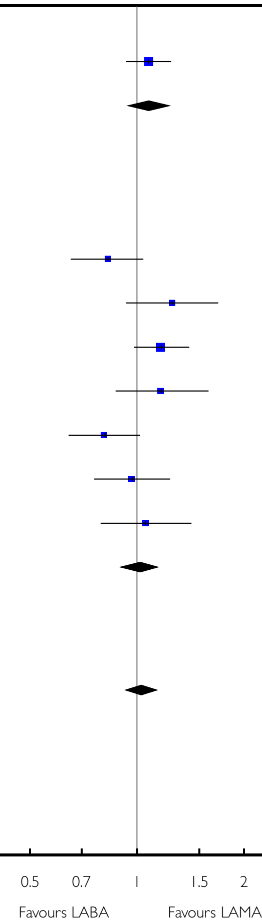
Analysis 6.4. Comparison 6 LAMA vs LABA, Outcome 4 SGRQ responders at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 4 SGRQ responders at 6 months

Study or subgroup	LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Decramer 2013	707/1421	673/1408		18.9 %	1.08 [0.93, 1.25]
Subtotal (95% CI)	**1421**	**1408**		**18.9 %**	**1.08 [0.93, 1.25]**
Total events: 707 (LAMA), 673 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
2 Low-risk					
Bateman 2013	514/880	279/443		12.4 %	0.83 [0.65, 1.04]
Brusasco 2003	174/356	153/354		9.3 %	1.26 [0.93, 1.69]
Buhl 2015a%b	465/955	427/954		16.2 %	1.17 [0.98, 1.40]
D'Urzo 2017	180/337	164/332		9.0 %	1.17 [0.87, 1.59]
Jones 2011	165/345	1042/1960		12.8 %	0.81 [0.64, 1.02]
Martinez 2017a	294/860	151/434		12.0 %	0.97 [0.76, 1.24]
Martinez 2017b	126/362	144/430		9.4 %	1.06 [0.79, 1.42]
Subtotal (95% CI)	**4095**	**4907**		**81.1 %**	**1.02 [0.89, 1.16]**
Total events: 1918 (LAMA), 2360 (LABA)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 12.31$, df = 6 (P = 0.06); $I^2 = 51\%$					
Test for overall effect: Z = 0.24 (P = 0.81)					
Total (95% CI)	**5516**	**6315**		**100.0 %**	**1.03 [0.92, 1.15]**
Total events: 2625 (LAMA), 3033 (LABA)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 12.80$, df = 7 (P = 0.08); $I^2 = 45\%$					
Test for overall effect: Z = 0.49 (P = 0.63)					
Test for subgroup differences: $Chi^2 = 0.37$, df = 1 (P = 0.54), $I^2 = 0.0\%$					



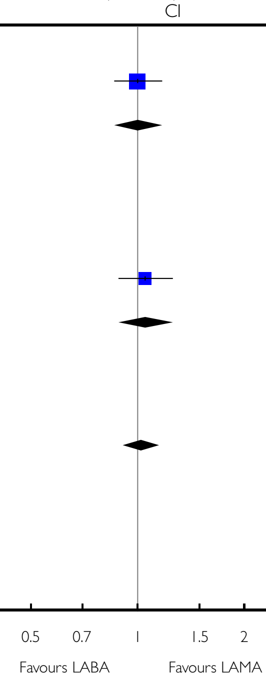
Analysis 6.5. Comparison 6 LAMA vs LABA, Outcome 5 SGRQ responders at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 5 SGRQ responders at 12 months

Study or subgroup	LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Decramer 2013	646/1314	626/1273		57.5 %	1.00 [0.86, 1.17]
Subtotal (95% CI)	**1314**	**1273**		**57.5 %**	**1.00 [0.86, 1.17]**
Total events: 646 (LAMA), 626 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 1.0)					
2 Low-risk					
Hanania 2017	490/1277	314/845		42.5 %	1.05 [0.88, 1.26]
Subtotal (95% CI)	**1277**	**845**		**42.5 %**	**1.05 [0.88, 1.26]**
Total events: 490 (LAMA), 314 (LABA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.56 (P = 0.57)					
Total (95% CI)	**2591**	**2118**		**100.0 %**	**1.02 [0.91, 1.15]**
Total events: 1136 (LAMA), 940 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.19$, df = 1 (P = 0.67); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.36 (P = 0.72)					
Test for subgroup differences: $Chi^2 = 0.19$, df = 1 (P = 0.67), $I^2 = 0.0\%$					



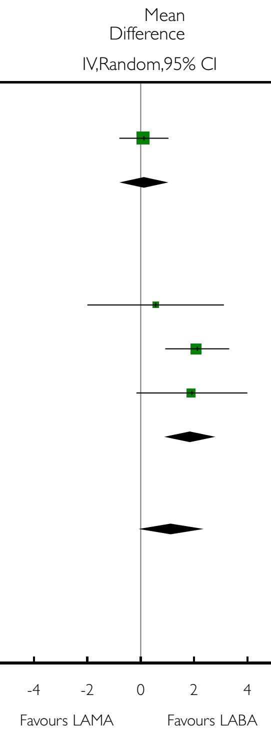
Analysis 6.6. Comparison 6 LAMA vs LABA, Outcome 6 Change from baseline in SGRQ at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 6 Change from baseline in SGRQ at 3 months

Study or subgroup	LAMA N	LAMA Mean(SD)	LABA N	LABA Mean(SD)	Weight	Mean Difference IV,Random,95% CI
1 High-risk						
Decramer 2013	1514	-4.5 (12.7)	1505	-4.6 (13)	35.1 %	0.10 [-0.82, 1.02]
Subtotal (95% CI)	**1514**		**1505**		**35.1 %**	**0.10 [-0.82, 1.02]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.21 (P = 0.83)						
2 Low-risk						
Bateman 2013	953	-7.56 (23.74)	476	-8.11 (23.05)	14.9 %	0.55 [-2.01, 3.11]
Buhl 2011	753	-3 (11.64)	743	-5.1 (12.06)	30.7 %	2.10 [0.90, 3.30]
Donohue 2010	415	-3.5 (17.66)	832	-5.4 (17.67)	19.2 %	1.90 [-0.18, 3.98]
Subtotal (95% CI)	**2121**		**2051**		**64.9 %**	**1.84 [0.87, 2.80]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.16$, df = 2 (P = 0.56); I^2 =0.0%						
Test for overall effect: Z = 3.74 (P = 0.00019)						
Total (95% CI)	**3635**		**3556**		**100.0 %**	**1.13 [-0.09, 2.34]**
Heterogeneity: $Tau^2 = 0.88$; $Chi^2 = 7.71$, df = 3 (P = 0.05); I^2 =61%						
Test for overall effect: Z = 1.82 (P = 0.069)						
Test for subgroup differences: $Chi^2 = 6.55$, df = 1 (P = 0.01), I^2 =85%						



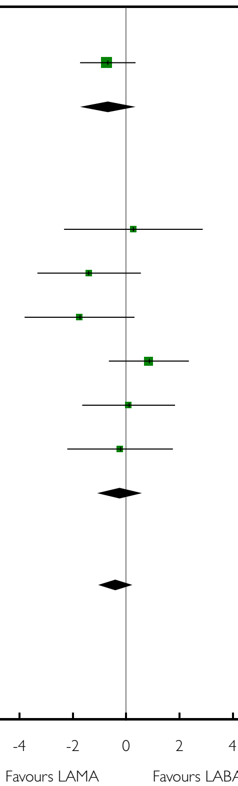
Analysis 6.7. Comparison 6 LAMA vs LABA, Outcome 7 Change from baseline in SGRQ at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 7 Change from baseline in SGRQ at 6 months

Study or subgroup	LAMA N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Decramer 2013	1432	-5.2 (13.8)	1416	-4.5 (14.4)		33.4 %	-0.70 [-1.74, 0.34]
Subtotal (95% CI)	**1432**		**1416**			**33.4 %**	**-0.70 [-1.74, 0.34]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.32 (P = 0.19)							
2 Low-risk							
Bateman 2013	880	-8.45 (23.36)	443	-8.72 (22.5)		6.0 %	0.27 [-2.33, 2.87]
Brusasco 2003	402	-4.2 (14.03)	405	-2.8 (14.09)		10.5 %	-1.40 [-3.34, 0.54]
D'Urzo 2014	257	-6.44 (11.86)	254	-4.7 (11.79)		9.5 %	-1.74 [-3.79, 0.31]
Martinez 2017a	739	-1.84 (11.94)	371	-2.7 (11.94)		17.4 %	0.86 [-0.63, 2.35]
Martinez 2017b	362	-2.2 (11.8)	352	-2.3 (11.82)		13.1 %	0.10 [-1.63, 1.83]
Singh 2014	327	-5.8 (12.84)	332	-5.58 (12.94)		10.2 %	-0.22 [-2.19, 1.75]
Subtotal (95% CI)	**2967**		**2157**			**66.6 %**	**-0.25 [-1.09, 0.58]**
Heterogeneity: Tau² = 0.15; Chi² = 5.82, df = 5 (P = 0.32); I² =14%							
Test for overall effect: Z = 0.59 (P = 0.55)							
Total (95% CI)	**4399**		**3573**			**100.0 %**	**-0.39 [-1.03, 0.25]**
Heterogeneity: Tau² = 0.04; Chi² = 6.34, df = 6 (P = 0.39); I² =5%							
Test for overall effect: Z = 1.19 (P = 0.23)							
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² =0.0%							



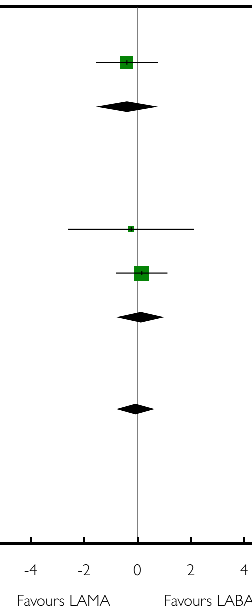
Analysis 6.8. Comparison 6 LAMA vs LABA, Outcome 8 Change from baseline in SGRQ at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 8 Change from baseline in SGRQ at 12 months

Study or subgroup	LAMA N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Decramer 2013	1325	-4.9 (14.8)	1281	-4.5 (15.5)		37.0 %	-0.40 [-1.56, 0.76]
Subtotal (95% CI)	**1325**		**1281**			**37.0 %**	**-0.40 [-1.56, 0.76]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.67 (P = 0.50)							
2 Low-risk							
D'Urzo 2017	337	-4.306 (15.55)	332	-4.06 (15.54)		9.0 %	-0.25 [-2.60, 2.11]
Hanania 2017	1277	-2.24 (11.051)	845	-2.4 (11.12)		54.0 %	0.16 [-0.80, 1.12]
Subtotal (95% CI)	**1614**		**1177**			**63.0 %**	**0.10 [-0.79, 0.99]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.10$, df = 1 (P = 0.75); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.22 (P = 0.82)							
Total (95% CI)	**2939**		**2458**			**100.0 %**	**-0.08 [-0.79, 0.62]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.55$, df = 2 (P = 0.76); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.23 (P = 0.82)							
Test for subgroup differences: $Chi^2 = 0.45$, df = 1 (P = 0.50), $I^2 = 0.0\%$							



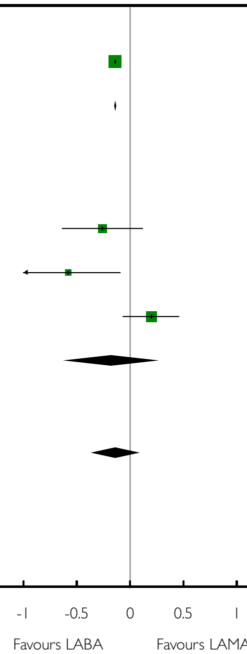
Analysis 6.9. Comparison 6 LAMA vs LABA, Outcome 9 TDI at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 9 TDI at 3 months

Study or subgroup	LAMA N	LAMA Mean(SD)	LABA N	LABA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Decramer 2013	1511	1.55 (0.15)	1513	1.69 (0.15)		40.6 %	-0.14 [-0.15, -0.13]
Subtotal (95% CI)	**1511**		**1513**			**40.6 %**	**-0.14 [-0.15, -0.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 25.66 (P < 0.00001)							
2 Low-risk							
Bateman 2013	953	1.92 (3.45)	476	2.18 (3.43)		19.3 %	-0.26 [-0.64, 0.12]
Buhl 2011	737	1.43 (4.83)	729	2.01 (4.81)		14.1 %	-0.58 [-1.07, -0.09]
Buhl 2015a%b	978	1.702 (3.033)	984	1.51 (3.043)		26.1 %	0.20 [-0.07, 0.46]
Subtotal (95% CI)	**2668**		**2189**			**59.4 %**	**-0.18 [-0.63, 0.27]**
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 8.82$, df = 2 (P = 0.01); I^2 =77%							
Test for overall effect: Z = 0.78 (P = 0.44)							
Total (95% CI)	**4179**		**3702**			**100.0 %**	**-0.14 [-0.37, 0.09]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 9.44$, df = 3 (P = 0.02); I^2 =68%							
Test for overall effect: Z = 1.18 (P = 0.24)							
Test for subgroup differences: $Chi^2 = 0.03$, df = 1 (P = 0.86), I^2 =0.0%							



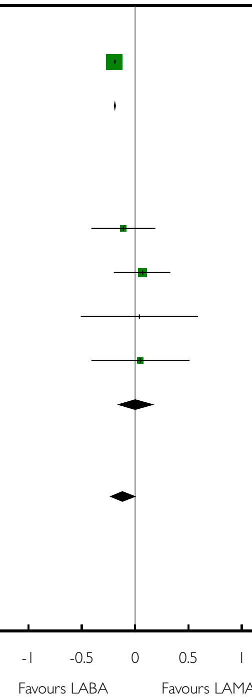
Analysis 6.10. Comparison 6 LAMA vs LABA, Outcome 10 TDI at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 10 TDI at 6 months

Study or subgroup	LAMA N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Decramer 2013	1436	1.46 (0.16)	1427	1.65 (0.16)		61.4 %	-0.19 [-0.20, -0.18]
Subtotal (95% CI)	**1436**		**1427**			**61.4 %**	**-0.19 [-0.20, -0.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 31.77 (P < 0.00001)							
2 Low-risk							
Bateman 2013	953	2.36 (2.79)	476	2.47 (2.76)		12.5 %	-0.11 [-0.41, 0.19]
Buhl 2015a%b	978	1.627 (3.002)	984	1.56 (3.01)		15.4 %	0.07 [-0.20, 0.33]
D'Urzo 2014	263	1.56 (3.24)	263	1.52 (3.24)		4.4 %	0.04 [-0.51, 0.59]
Singh 2014	331	2.11 (3.09)	333	2.06 (2.92)		6.3 %	0.05 [-0.41, 0.51]
Subtotal (95% CI)	**2525**		**2056**			**38.6 %**	**0.00 [-0.17, 0.18]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.81, df = 3 (P = 0.85); I^2 =0.0%							
Test for overall effect: Z = 0.04 (P = 0.96)							
Total (95% CI)	**3961**		**3483**			**100.0 %**	**-0.12 [-0.24, 0.01]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 5.55, df = 4 (P = 0.24); I^2 =28%							
Test for overall effect: Z = 1.87 (P = 0.061)							
Test for subgroup differences: Chi^2 = 4.74, df = 1 (P = 0.03), I^2 =79%							



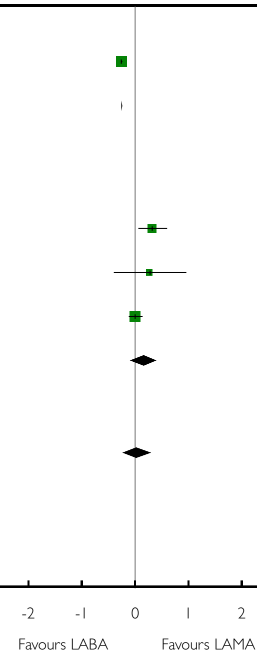
Analysis 6.11. Comparison 6 LAMA vs LABA, Outcome 11 TDI at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 11 TDI at 12 months

Study or subgroup	LAMA N	LAMA Mean(SD)	LABA N	LABA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Decramer 2013	1322	1.75 (0.16)	1288	2.01 (0.17)		33.6 %	-0.26 [-0.27, -0.25]
Subtotal (95% CI)	**1322**		**1288**			**33.6 %**	**-0.26 [-0.27, -0.25]**
Heterogeneity: not applicable							
Test for overall effect: Z = 40.21 (P < 0.00001)							
2 Low-risk							
Buhl 2015a%b	978	1.736 (3.159)	984	1.41 (3.168)		24.6 %	0.32 [0.05, 0.60]
D'Urzo 2017	337	1.596 (4.42)	332	1.32 (4.48)		10.7 %	0.27 [-0.40, 0.95]
Hanania 2017	1309	0.3 (1.54)	871	0.3 (1.51)		31.1 %	0.0 [-0.13, 0.13]
Subtotal (95% CI)	**2624**		**2187**			**66.4 %**	**0.15 [-0.11, 0.40]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 4.63$, df = 2 (P = 0.10); $I^2 = 57\%$							
Test for overall effect: Z = 1.12 (P = 0.26)							
Total (95% CI)	**3946**		**3475**			**100.0 %**	**0.02 [-0.25, 0.29]**
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 34.08$, df = 3 (P<0.00001); $I^2 = 91\%$							
Test for overall effect: Z = 0.16 (P = 0.87)							
Test for subgroup differences: $Chi^2 = 9.67$, df = 1 (P = 0.00), $I^2 = 90\%$							



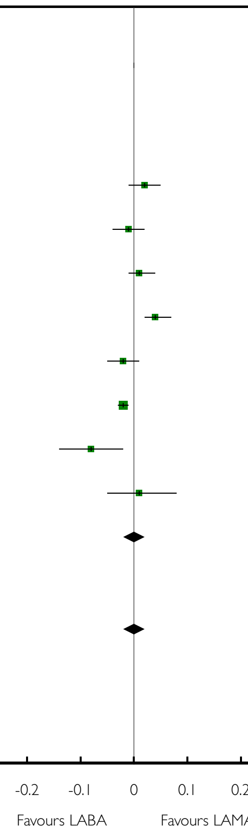
Analysis 6.12. Comparison 6 LAMA vs LABA, Outcome 12 Change from baseline in FEV1 at 3 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 12 Change from baseline in FEV1 at 3 months

Study or subgroup	LAMA N	LAMA Mean(SD)	LABA N	LABA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Briggs 2005	328	0.088 (0.181)	325	0.07 (0.198)		13.4 %	0.02 [-0.01, 0.05]
Buhl 2011	595	0.12 (0.244)	562	0.13 (0.237)		13.7 %	-0.01 [-0.04, 0.02]
Buhl 2015a	520	0.07 (0.205)	519	0.06 (0.205)		14.4 %	0.01 [-0.01, 0.04]
Buhl 2015b	498	0.088 (0.201)	503	0.05 (0.202)		14.4 %	0.04 [0.02, 0.07]
Donohue 2010	349	0.15 (0.227)	700	0.17 (0.263)		12.9 %	-0.02 [-0.05, 0.01]
Hoshino 2013	15	0.044 (0.012)	14	0.06 (0.021)		17.2 %	-0.02 [-0.03, -0.01]
Hoshino 2014	16	0.056 (0.119)	20	0.14 (0.0149)		7.3 %	-0.08 [-0.14, -0.02]
Mahler 2016	229	0.104 (0.34)	227	0.09 (0.339)		6.7 %	0.01 [-0.05, 0.08]
Subtotal (95% CI)	**2550**		**2870**			**100.0 %**	**0.00 [-0.02, 0.02]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 29.49$, df = 7 (P = 0.00012); I^2 =76%							
Test for overall effect: Z = 0.21 (P = 0.84)							
Total (95% CI)	**2550**		**2870**			**100.0 %**	**0.00 [-0.02, 0.02]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 29.49$, df = 7 (P = 0.00012); I^2 =76%							
Test for overall effect: Z = 0.21 (P = 0.84)							
Test for subgroup differences: Not applicable							



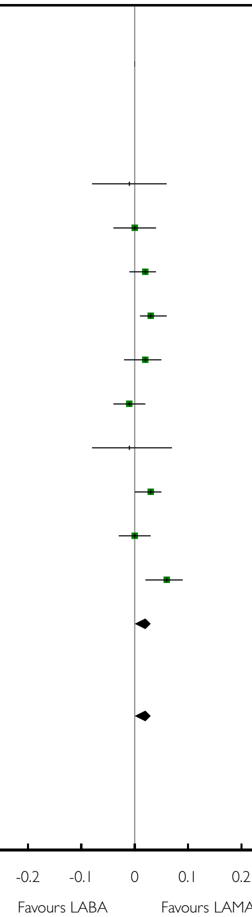
Analysis 6.13. Comparison 6 LAMA vs LABA, Outcome 13 Change from baseline in FEV1 at 6 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 13 Change from baseline in FEV1 at 6 months

Study or subgroup	LAMA N	Mean(SD)	LABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Bateman 2013	424	0.08 (0.494)	435	0.09 (0.501)		3.3 %	-0.01 [-0.08, 0.06]
Brusasco 2003	209	-0.013 (0.188)	213	-0.01 (0.19)		9.1 %	0.00 [-0.04, 0.04]
Buhl 2015a	520	0.05 (0.205)	519	0.03 (0.205)		14.4 %	0.02 [-0.01, 0.04]
Buhl 2015b	498	0.068 (0.201)	503	0.03 (0.202)		14.4 %	0.03 [0.01, 0.06]
D'Urzo 2014	266	0.066 (0.196)	268	0.05 (0.196)		10.1 %	0.02 [-0.02, 0.05]
Donohue 2010	321	0.13 (0.235)	651	0.14 (0.277)		10.1 %	-0.01 [-0.04, 0.02]
Mahler 2016	229	0.079 (0.4)	227	0.09 (0.398)		2.8 %	-0.01 [-0.08, 0.07]
Martinez 2017a	734	0.09 (0.2)	367	0.06 (0.203)		14.2 %	0.03 [0.00, 0.05]
Martinez 2017b	367	0.063 (0.209)	350	0.06 (0.208)		11.4 %	0.00 [-0.03, 0.03]
Singh 2014	332	0.056 (0.219)	337	0 (0.22)		10.1 %	0.06 [0.02, 0.09]
Subtotal (95% CI)	**3900**		**3870**			**100.0 %**	**0.02 [0.00, 0.03]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 13.43$, df = 9 (P = 0.14); $I^2 = 33\%$							
Test for overall effect: Z = 2.69 (P = 0.0071)							
Total (95% CI)	**3900**		**3870**			**100.0 %**	**0.02 [0.00, 0.03]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 13.43$, df = 9 (P = 0.14); $I^2 = 33\%$							
Test for overall effect: Z = 2.69 (P = 0.0071)							
Test for subgroup differences: Not applicable							



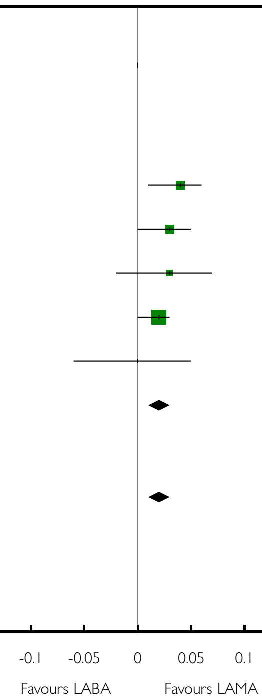
Analysis 6.14. Comparison 6 LAMA vs LABA, Outcome 14 Change from baseline in FEV1 at 12 months.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 14 Change from baseline in FEV1 at 12 months

Study or subgroup	LAMA N	LAMA Mean(SD)	LABA N	LABA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 High-risk							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Low-risk							
Buhl 2015a	520	0.036 (0.205)	519	0 (0.205)		19.5 %	0.04 [0.01, 0.06]
Buhl 2015b	498	0.04 (0.201)	503	0.01 (0.202)		19.5 %	0.03 [0.00, 0.05]
D'Urzo 2017	337	0.03 (0.275)	332	0 (0.273)		7.0 %	0.03 [-0.02, 0.07]
Hanania 2017	1317	0.086 (0.181)	871	0.07 (0.181)		50.5 %	0.02 [0.00, 0.03]
Mahler 2016	229	0.056 (0.319)	227	0.06 (0.321)		3.5 %	0.00 [-0.06, 0.05]
Subtotal (95% CI)	**2901**		**2452**			**100.0 %**	**0.02 [0.01, 0.03]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.49, df = 4 (P = 0.65); I^2 =0.0%							
Test for overall effect: Z = 4.17 (P = 0.000030)							
Total (95% CI)	**2901**		**2452**			**100.0 %**	**0.02 [0.01, 0.03]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.49, df = 4 (P = 0.65); I^2 =0.0%							
Test for overall effect: Z = 4.17 (P = 0.000030)							
Test for subgroup differences: Not applicable							



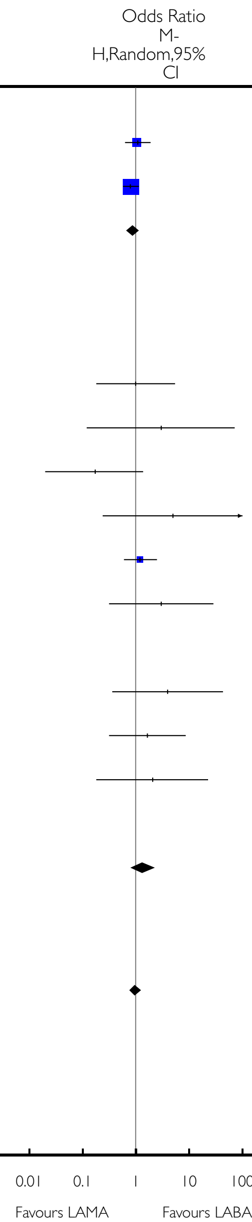
Analysis 6.15. Comparison 6 LAMA vs LABA, Outcome 15 Mortality.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 15 Mortality

Study or subgroup	LAMA n/N	LABA n/N	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk				
Decramer 2013	26/1718	24/1721	20.2 %	1.09 [0.62, 1.90]
Vogelmeier 2011	64/3707	78/3669	56.7 %	0.81 [0.58, 1.13]
Subtotal (95% CI)	**5425**	**5390**	**76.9 %**	**0.87 [0.66, 1.16]**
Total events: 90 (LAMA), 102 (LABA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.79$, df = 1 (P = 0.37); I^2 =0.0%				
Test for overall effect: Z = 0.92 (P = 0.36)				
2 Low-risk				
Bateman 2013	4/953	2/476	2.2 %	1.00 [0.18, 5.47]
Briggs 2005	1/328	0/325	0.6 %	2.98 [0.12, 73.46]
Brusasco 2003	1/402	6/405	1.4 %	0.17 [0.02, 1.38]
Buhl 2011	2/801	0/797	0.7 %	4.99 [0.24, 104.05]
Buhl 2015a%b	17/1033	14/1038	12.4 %	1.22 [0.60, 2.50]
D'Urzo 2014	3/337	1/332	1.2 %	2.97 [0.31, 28.73]
D'Urzo 2017	0/194	0/192		Not estimable
Donohue 2010	2/415	1/832	1.1 %	4.02 [0.36, 44.51]
Hanania 2017	5/1341	2/890	2.3 %	1.66 [0.32, 8.58]
Mahler 2016	2/251	1/256	1.1 %	2.05 [0.18, 22.73]
Vogelmeier 2008	0/221	0/210		Not estimable
Subtotal (95% CI)	**6276**	**5753**	**23.1 %**	**1.33 [0.79, 2.25]**
Total events: 37 (LAMA), 27 (LABA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.35$, df = 8 (P = 0.61); I^2 =0.0%				
Test for overall effect: Z = 1.07 (P = 0.28)				
Total (95% CI)	**11701**	**11143**	**100.0 %**	**0.96 [0.75, 1.24]**
Total events: 127 (LAMA), 129 (LABA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 9.02$, df = 10 (P = 0.53); I^2 =0.0%				
Test for overall effect: Z = 0.29 (P = 0.77)				
Test for subgroup differences: $Chi^2 = 1.91$, df = 1 (P = 0.17), I^2 =48%				



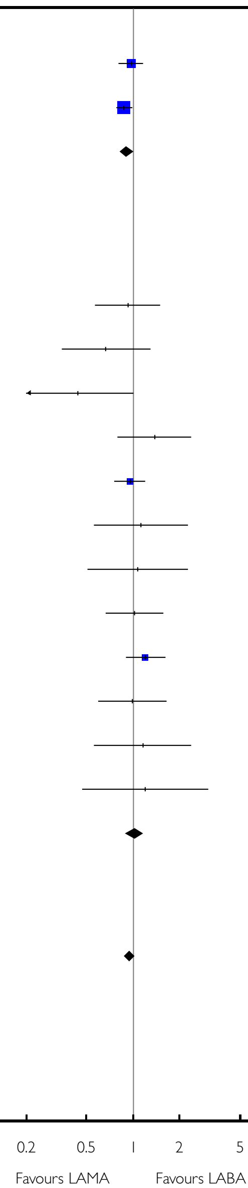
Analysis 6.16. Comparison 6 LAMA vs LABA, Outcome 16 Total SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 16 Total SAE

Study or subgroup	LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Decramer 2013	255/1718	263/1721		19.2 %	0.97 [0.80, 1.16]
Vogelmeier 2011	545/3707	606/3669		42.2 %	0.87 [0.77, 0.99]
Subtotal (95% CI)	**5425**	**5390**		**61.4 %**	**0.90 [0.81, 1.00]**
Total events: 800 (LAMA), 869 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.81$, df = 1 (P = 0.37); I^2 =0.0%					
Test for overall effect: Z = 1.98 (P = 0.048)					
2 Low-risk					
Bateman 2013	48/953	26/476		2.8 %	0.92 [0.56, 1.50]
BI 205.137 2001	16/193	23/192		1.5 %	0.66 [0.34, 1.30]
Briggs 2005	8/328	18/325		0.9 %	0.43 [0.18, 1.00]
Buhl 2011	30/801	22/797		2.1 %	1.37 [0.78, 2.40]
Buhl 2015a%b	172/1033	181/1038		12.8 %	0.95 [0.75, 1.19]
D'Urzo 2014	17/337	15/332		1.3 %	1.12 [0.55, 2.29]
D'Urzo 2017	15/194	14/192		1.2 %	1.07 [0.50, 2.27]
Donohue 2010	34/415	67/832		3.6 %	1.02 [0.66, 1.57]
Hanania 2017	139/1341	78/890		7.9 %	1.20 [0.90, 1.61]
Mahler 2016	33/251	34/256		2.5 %	0.99 [0.59, 1.65]
Singh 2014	16/385	14/384		1.3 %	1.15 [0.55, 2.38]
Vogelmeier 2008	10/221	8/210		0.7 %	1.20 [0.46, 3.09]
Subtotal (95% CI)	**6452**	**5924**		**38.6 %**	**1.01 [0.88, 1.15]**
Total events: 538 (LAMA), 500 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.83$, df = 11 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 0.14 (P = 0.89)					
Total (95% CI)	**11877**	**11314**		**100.0 %**	**0.94 [0.87, 1.02]**
Total events: 1338 (LAMA), 1369 (LABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 11.43$, df = 13 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 1.47 (P = 0.14)					
Test for subgroup differences: $Chi^2 = 1.79$, df = 1 (P = 0.18), I^2 =44%					



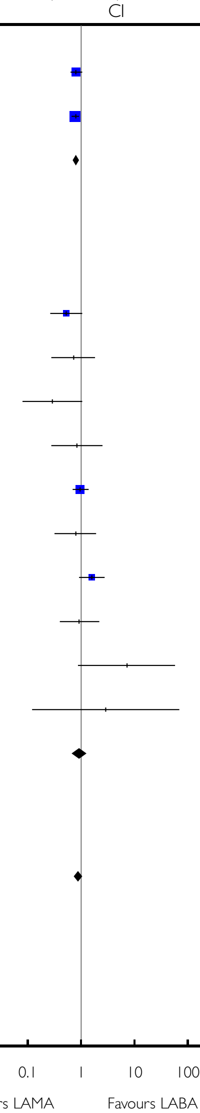
Analysis 6.17. Comparison 6 LAMA vs LABA, Outcome 17 COPD SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 17 COPD SAE

Study or subgroup	LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Decramer 2013	121/1718	147/1721		22.3 %	0.81 [0.63, 1.04]
Vogelmeier 2011	270/3707	335/3669		28.4 %	0.78 [0.66, 0.92]
Subtotal (95% CI)	**5425**	**5390**		**50.6 %**	**0.79 [0.69, 0.91]**
Total events: 391 (LAMA), 482 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 3.31 (P = 0.00094)					
2 Low-risk					
Bateman 2013	16/953	15/476		5.9 %	0.52 [0.26, 1.07]
BI 205.137 2001	8/193	11/192		3.7 %	0.71 [0.28, 1.81]
Briggs 2005	3/328	10/325		2.0 %	0.29 [0.08, 1.07]
Buhl 2011	6/801	7/797		2.8 %	0.85 [0.28, 2.55]
Buhl 2015a%b	65/1033	67/1038		16.1 %	0.97 [0.68, 1.38]
Donohue 2010	7/415	18/832		4.1 %	0.78 [0.32, 1.87]
Hanania 2017	45/1341	19/890		9.1 %	1.59 [0.92, 2.74]
Mahler 2016	11/251	12/256		4.5 %	0.93 [0.40, 2.15]
Singh 2014	7/385	1/384		0.8 %	7.09 [0.87, 57.93]
Vogelmeier 2008	1/221	0/210		0.3 %	2.86 [0.12, 70.70]
Subtotal (95% CI)	**5921**	**5400**		**49.4 %**	**0.91 [0.65, 1.27]**
Total events: 169 (LAMA), 160 (LABA)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 13.95, df = 9 (P = 0.12); I^2 =35%					
Test for overall effect: Z = 0.56 (P = 0.57)					
Total (95% CI)	**11346**	**10790**		**100.0 %**	**0.86 [0.71, 1.04]**
Total events: 560 (LAMA), 642 (LABA)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 15.72, df = 11 (P = 0.15); I^2 =30%					
Test for overall effect: Z = 1.58 (P = 0.11)					
Test for subgroup differences: Chi^2 = 0.57, df = 1 (P = 0.45), I^2 =0.0%					



Analysis 6.18. Comparison 6 LAMA vs LABA, Outcome 18 Cardiac SAE.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 18 Cardiac SAE

Study or subgroup	LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Decramer 2013	51/1718	54/1721		29.0 %	0.94 [0.64, 1.39]
Vogelmeier 2011	63/3707	50/3669		31.3 %	1.25 [0.86, 1.82]
Subtotal (95% CI)	**5425**	**5390**		**60.4 %**	**1.09 [0.83, 1.44]**
Total events: 114 (LAMA), 104 (LABA)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.05, df = 1 (P = 0.31); I^2 =4%					
Test for overall effect: Z = 0.63 (P = 0.53)					
2 Low-risk					
Bateman 2013	11/953	8/476		5.2 %	0.68 [0.27, 1.71]
Buhl 2011	6/801	6/797		3.4 %	0.99 [0.32, 3.10]
Buhl 2015a%b	19/1033	15/1038		9.4 %	1.28 [0.65, 2.53]
D'Urzo 2014	1/337	3/332		0.9 %	0.33 [0.03, 3.15]
D'Urzo 2017	4/194	2/192		1.5 %	2.00 [0.36, 11.05]
Donohue 2010	10/415	16/832		6.9 %	1.26 [0.57, 2.80]
Hanania 2017	22/1341	5/890		4.6 %	2.95 [1.11, 7.82]
Mahler 2016	9/251	12/256		5.6 %	0.76 [0.31, 1.83]
Singh 2014	1/385	0/384		0.4 %	3.00 [0.12, 73.87]
Vogelmeier 2008	3/221	3/210		1.7 %	0.95 [0.19, 4.76]
Subtotal (95% CI)	**5931**	**5407**		**39.6 %**	**1.16 [0.83, 1.61]**
Total events: 86 (LAMA), 70 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 7.92, df = 9 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 0.86 (P = 0.39)					
Total (95% CI)	**11356**	**10797**		**100.0 %**	**1.12 [0.91, 1.38]**

0.01 0.1 1 10 100

Favours LAMA Favours LABA

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Study or subgroup	LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Total events: 200 (LAMA), 174 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 9.01, df = 11 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 1.04 (P = 0.30)					
Test for subgroup differences: Chi^2 = 0.07, df = 1 (P = 0.80), I^2 =0.0%					

0.01 0.1 1 10 100

Favours LAMA Favours LABA

Analysis 6.19. Comparison 6 LAMA vs LABA, Outcome 19 Dropuouts due to adverse events.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 19 Dropuouts due to adverse events

Study or subgroup	LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk					
Decramer 2013	96/1718	101/1721		16.7 %	0.95 [0.71, 1.27]
Vogelmeier 2011	264/3707	292/3669		33.3 %	0.89 [0.75, 1.05]
Subtotal (95% CI)	**5425**	**5390**		**49.9 %**	**0.90 [0.78, 1.05]**
Total events: 360 (LAMA), 393 (LABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.16, df = 1 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 1.35 (P = 0.18)					
2 Low-risk					
Bateman 2013	24/953	24/476		5.0 %	0.49 [0.27, 0.87]
Buhl 2011	27/801	31/797		5.9 %	0.86 [0.51, 1.46]
Buhl 2015a%b	43/1033	51/1038		9.0 %	0.84 [0.55, 1.27]
D'Urzo 2014	16/337	14/332		3.1 %	1.13 [0.54, 2.36]
D'Urzo 2017	6/194	4/192		1.1 %	1.50 [0.42, 5.40]

0.1 0.2 0.5 1 2 5 10

Favours LAMA Favours LABA

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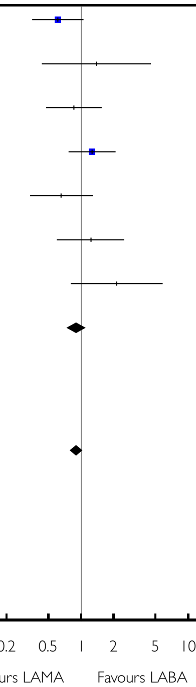
Study or subgroup	LAMA n/N	LABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Donohue 2010	17/415	55/832		5.3 %	0.60 [0.35, 1.05]
Hanania 2017	10/389	4/213		1.3 %	1.38 [0.43, 4.45]
Mahler 2016	22/251	26/256		4.7 %	0.85 [0.47, 1.54]
Martinez 2017a	55/902	22/452		6.3 %	1.27 [0.76, 2.11]
Martinez 2017b	14/439	21/438		3.5 %	0.65 [0.33, 1.30]
Singh 2014	17/385	14/384		3.2 %	1.22 [0.59, 2.51]
Vogelmeier 2008	13/221	6/210		1.8 %	2.13 [0.79, 5.70]
Subtotal (95% CI)	**6320**	**5620**		**50.1 %**	**0.89 [0.72, 1.10]**
Total events: 264 (LAMA), 272 (LABA)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 14.13$, df = 11 (P = 0.23); I^2 =22%					
Test for overall effect: Z = 1.06 (P = 0.29)					
Total (95% CI)	**11745**	**11010**		**100.0 %**	**0.89 [0.78, 1.02]**
Total events: 624 (LAMA), 665 (LABA)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 14.33$, df = 13 (P = 0.35); I^2 =9%					
Test for overall effect: Z = 1.64 (P = 0.10)					
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.92), I^2 =0.0%					



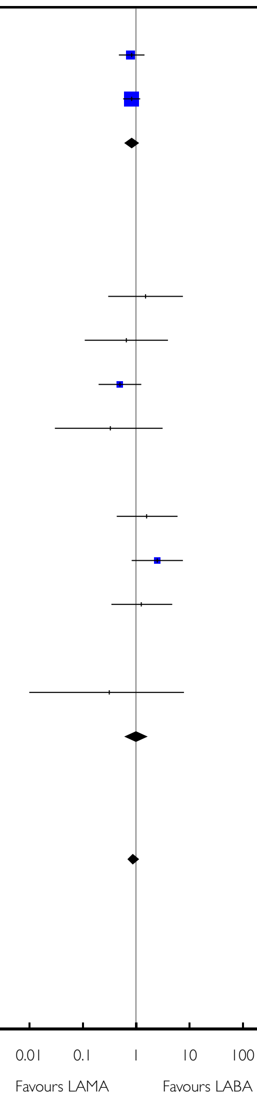
Analysis 6.20. Comparison 6 LAMA vs LABA, Outcome 20 Pneumonia.

Review: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis

Comparison: 6 LAMA vs LABA

Outcome: 20 Pneumonia

Study or subgroup	LAMA n/N	LABA n/N	Weight	Odds Ratio M-H,Random,95% CI
1 High-risk				
Decramer 2013	24/1718	29/1721	22.4 %	0.83 [0.48, 1.43]
Vogelmeier 2011	54/3707	64/3669	49.9 %	0.83 [0.58, 1.20]
Subtotal (95% CI)	**5425**	**5390**	**72.3 %**	**0.83 [0.61, 1.13]**
Total events: 78 (LAMA), 93 (LABA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.20 (P = 0.23)				
2 Low-risk				
Bateman 2013	6/953	2/476	2.6 %	1.50 [0.30, 7.47]
Buhl 2011	2/801	3/797	2.1 %	0.66 [0.11, 3.98]
Buhl 2015a%b	7/1033	14/1038	8.0 %	0.50 [0.20, 1.24]
D'Urzo 2014	1/337	3/332	1.3 %	0.33 [0.03, 3.15]
D'Urzo 2017	0/194	0/192		Not estimable
Donohue 2010	4/415	5/832	3.8 %	1.61 [0.43, 6.03]
Hanania 2017	15/1341	4/890	5.4 %	2.51 [0.83, 7.57]
Mahler 2016	5/251	4/256	3.8 %	1.28 [0.34, 4.82]
Singh 2014	0/385	0/384		Not estimable
Vogelmeier 2008	0/221	1/210	0.6 %	0.32 [0.01, 7.78]
Subtotal (95% CI)	**5931**	**5407**	**27.7 %**	**1.01 [0.61, 1.69]**
Total events: 40 (LAMA), 36 (LABA)				
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 7.40$, df = 7 (P = 0.39); $I^2 = 5\%$				
Test for overall effect: Z = 0.04 (P = 0.97)				
Total (95% CI)	**11356**	**10797**	**100.0 %**	**0.88 [0.68, 1.13]**
Total events: 118 (LAMA), 129 (LABA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 7.83$, df = 9 (P = 0.55); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.01 (P = 0.31)				
Test for subgroup differences: $Chi^2 = 0.42$, df = 1 (P = 0.52), $I^2 = 0.0\%$				



ADDITIONAL TABLES

Table 1. Study characteristics of included trials

High-risk group								
Study	**Number of participants**	**Study duration (weeks)**	**Arms included (drug, dose in μg, dosing frequency)**	**Mean age (years)**	**Male (%)**	**Current smoker (%)**	**Prebronchodilator FEV1 (L)**	**Bronchial reversibility (%)**
Aaron 2007	304	52	Tio 18 once daily + SAL 50 twice daily Tio 18 once daily	68	56	26	1.01	NR
Agusti 2014	528	12	FP/SAL 500/50 twice daily FF/VI 100/25 once daily	63	82	NR	1.29	11.8
Anzueto 2009	797	52	FP/SAL 250/50 twice daily SAL 50 twice daily	65	54	43	0.98	21
Calverley 2003	509	52	BUD/FM 320/9 twice daily FM 9 twice daily	63	76	35	0.99	NR
Calverley 2003 TRISTAN	730	52	FP/SAL 500/50 twice daily SAL 50 twice daily	63	75	51	1.28	7.8
Calverley 2010	703	48	BDP/FM 200/12 twice daily BUD/FM 400/12 twice daily	64	81	37	1.15	NR

Table 1. Study characteristics of included trials *(Continued)*

			FM 12 twice daily					
COMBINE 2017	222	24	FP 250 twice daily + SAL 50 twice daily BUD 400 twice daily + IND 150 once daily	67	57	NR	NR	NR
Decramer 2013	3439	52	IND 150 once daily Tio 18 once daily	64	77	34	NR	NR
Ferguson 2008	776	52	FP/SAL 250/50 twice daily SAL 50 twice daily	65	55	39	0.94	24.2
Ferguson 2017	1219	26	BUD/FM 320/9 twice daily FM 9 twice daily	64	57	NR	NR	NR
Fukuchi 2013	1293	12	BUD/FM 320/9 twice daily FM 9 twice daily	65	89	34	0.96	13.6
Hagedorn 2013	213	52	FP/SAL 500/50 twice daily FP 500 + SAL 50 twice daily	65	71	29	1.05	NR
Kardos 2007	994	44	FP/SAL 500/50 twice daily SAL 50 twice daily	64	76	42	1.13	7

Table 1. **Study characteristics of included trials** *(Continued)*

Ohar 2014	639	26	FP/ SAL 250/50 twice daily SAL 50 twice daily	63	91	NR	1.11	13.6
Pepin 2014	257	12	FF/VI 100/25 once daily Tio 18 once daily	67	86	46	1.27	8.5
Rennard 2009	1483	52	BUD/FM 320/9 twice daily BUD/FM 160/9 twice daily FM 9 twice daily	63	64	42	1.00	NR
Sarac 2016	44	52	FP/ SAL 500/50 twice daily Tio 18 once daily	67	95	NR	NR	NR
SCO40041 2008	186	156	FP/ SAL 250/50 twice daily SAL 50 twice daily	66	61	42	1.14	15.2
Sharafkhaneh 2012	1218	52	BUD/FM 320/9 twice daily BUD/FM 160/9 twice daily FM 9 twice daily	63	62	36	1.00	NR
Szafranski 2003	409	52	BUD/FM 320/9 twice daily FM 9 twice daily	64	76	34	0.98	NR

Table 1. Study characteristics of included trials (*Continued)*

Tashkin 2008	842	24	BUD/FM 320/9 twice daily BUD/FM 160/9 twice daily FM 9 twice daily	63	66	45	1.04	NR
Vogelmeier 2011	7376	52	SAL 50 twice daily Tio 18 once daily	63	75	48	NR	NR
Wedzicha 2008	1323	104	FP/SAL 250/50 twice daily Tio 18 once daily	65	83	38	1.05	6.7
Wedzicha 2013	2206	64	IND/Glyco 110/50 once daily Glyco 50 once daily Tio 18 once daily	63	75	38	0.90	18.3
Wedzicha 2014	1197	48	BDP/FM 200/12 twice daily FM 12 twice daily	64	69	40	1.05	10.8
Wedzicha 2016	3358	52	IND/Glyco 110/50 once daily FP/SAL 500/50 twice daily	65	76	40	1.00	22.4
Low-risk group								
Study	**Number of participants**	**Study duration (weeks)**	**Arms included (drug, dose in μg, dosing**	**Mean age (years)**	**Male (%)**	**Current smoker (%)**	**Prebronchodilator FEV1 (L)**	**Bronchial reversibility (%)**

Table 1. Study characteristics of included trials *(Continued)*

			frequency)					
Asai 2013	158	52	IND/Glyco 110/50 once daily Tio 18 once daily	69	96	NR	NR	NR
BI 205.137 2001	385	12	SAL 50 twice daily Tio 18 once daily	NR	NR	NR	NR	NR
Bateman 2013	1903	26	IND/Glyco 110/50 once daily Glyco 50 once daily Tio 18 once daily IND 150 once daily	64	75	40	1.30	20.4
Bogdan 2011	405	12	FM 4.5 twice daily FM 9 twice daily	67	87	NR	1.30	10.6
Briggs 2005	653	12	SAL 50 twice daily Tio 18 once daily	64	67	36	1.05	NR
Brusasco 2003	807	24	SAL 50 twice daily Tio 18 once daily	64	76	NR	1.09	NR
Buhl 2011	1598	12	IND 150 once daily Tio 18 once daily	64	69	45	1.33	13.9
Buhl 2015a&b	3100	52	Tio/Olo 5/5 once daily Tio 5 once daily Olo 5 once daily	64	73	37	1.20	14.2

Table 1. **Study characteristics of included trials** *(Continued)*

Buhl 2015c	934	26	IND/Glyco 110/50 once daily Tio 18 once daily + FM 12 twice daily	63	66	49	1.33	19.4
Calverley 2007	3054	156	FP/SAL 500/50 twice daily SAL 50 twice daily	65	75	43	1.11	10.2
Cazzola 2007	52	12	FP/SAL 500/50 twice daily Tio 18 once daily	65	90	38	NR	12.3
Chapman 2014	657	12	Glyco 50 once daily Tio 18 once daily	64	74	45	NR	NR
COSMOS-J 2016	262	24	FP/SAL 250/50 twice daily Tio 18 once daily	68	95	40	NR	NR
Covelli 2016	623	12	FF/VI 100/25 once daily TIO 18 once daily	63	65	52	1.35	13
D'Urzo 2014	994	24	ACL/FM 400/12 twice daily ACL 400 twice daily FM 12 twice daily	64	52	51	1.35	17.4
D'Urzo 2017	568	52	ACL/FM 400/12 twice daily	63	50	56	1.34	18.3

Table 1. Study characteristics of included trials *(Continued)*

			ACL 400 twice daily FM 12 twice daily					
Dahl 2010	871	52	IND 300 once daily FM 12 twice daily	64	80	NR	1.29	10
Decramer 2014a	420	24	UMEC/VI 62.5/25 once daily Tio 18 once daily	63	69	47	1.31	11.6
Decramer 2014b	432	24	UMEC/VI 62.5/25 once daily Tio 18 once daily	65	68	45	1.17	15.2
Donohue 2010	1247	26	IND150 once daily IND 300 once daily Tio 18 once daily	64	63	NR	1.50	15.5
Donohue 2013	831	24	UMEC/VI 62.5/25 once daily UMEC 62.5 once daily	63	71	50	1.23	13.9
Donohue 2015a	706	12	UMEC/VI 62.5/25 once daily FP/SAL 250/50 twice daily	63	70	43	1.32	11.3
Donohue 2015b	697	12	UMEC/VI 62.5/25 once daily FP/SAL 250/50 twice daily	64	76	52	1.34	13.3

Table 1. **Study characteristics of included trials** *(Continued)*

Donohue 2016a	590	56	ACL/ FM 400/12 twice daily FM 12 twice daily	64	55	46	1.31	NR
Dransfield 2014	1858	12	FP/ SAL 250/50 twice daily FF/VI 100/25 once daily	61	69	55	1.34	12
Feldman 2016	1017	12	UMEC 62.5 once daily Tio 18 once daily	64	72	51	1.36	12.1
Ferguson 2016	410	52	IND/Glyco 27.5/15.6 twice daily IND 75 once daily	63	68	51	1.25	22.4
GLOW4 2012	163	52	Glyco 50 once daily Tio 18 once daily	69	98	NR	NR	NR
Hanania 2003	355	24	FP/ SAL 250/50 twice daily SAL 50 twice daily	64	60	47	1.21	20.7
Hoshino 2013	45	16	FP/ SAL 250/50 twice daily Tio 18 once daily SAL 50 twice daily	71	87	NR	1.35	NR
Hoshino 2014	54	16	TIO 18 once daily + IND 150 once daily IND 150	71	93	NR	1.53	NR

Table 1. Study characteristics of included trials *(Continued)*

			once daily Tio 18 once daily					
Hoshino 2015	43	16	TIO 18 once daily + IND 150 once daily FP/SAL 250/50 twice daily	71	84	NR	1.37	NR
Kalberg 2016	961	12	UMEC/VI 62.5/25 once daily Tio 18 once daily + IND 150 once daily	64	73	43	1.23	12.3
Kerwin 2012a	792	52	Glyco 50 once daily Tio 18 once daily	64	64	45	1.30	16.3
Kerwin 2017	494	12	UMEC/VI 62.5/25 once daily Tio 18 once daily	64	66	50	1.65	7.9
Koch 2014	919	48	Olo 5 once daily FM 12 twice daily	64	80	34	1.26	12.3
Kornmann 2011	667	26	IND 150 once daily SAL 50 twice daily	63	74	46	1.35	11.5
Koser 2010	247	12	FP/SAL 250/50 twice daily FP/SAL 230/42 twice daily	63	53	62	1.27	12.7

Table 1. **Study characteristics of included trials** *(Continued)*

Mahler 2002	325	24	FP/ SAL 500/50 twice daily SAL 50 twice daily	63	63	46	1.25	20.9
Mahler 2012a	1131	12	Tio 18 once daily + IND 150 once daily Tio 18 once daily	64	69	38	1.15	16.9
Mahler 2012b	1142	12	Tio 18 once daily + IND 150 once daily Tio 18 once daily	63	66	40	1.14	16.4
Mahler 2015a; Mahler 2015b	1530	12	IND/Glyco 27.5/15.6 twice daily Glyco 15.6 twice daily	64	64	52	1.27	22.8
Mahler 2016	507	52	IND 75 once daily Glyco 15.6 twice daily	63	57	55	1.25	21.2
Maleki-Yazdi 2014	905	24	UMEC/ VI 62.5/25 once daily Tio 18 once daily	62	68	57	1.26	13.4
Martinez 2017a	1880	24	Glyco/FM 18/9.6 twice daily Glyco 18 twice daily Tio 18 once daily FM 9.6 twice daily	63	56	54	1.25	19.8

Table 1. Study characteristics of included trials *(Continued)*

Martinez 2017b	1387	24	Glyco/FM 18/9.6 twice daily Glyco 18 twice daily FM 9.6 twice daily	63	55	54	NR	19.2
NCT0087669 2011	186	52	IND 300 once daily SAL 50 twice daily	69	95	NR	NR	NR
NCT0153626 2014	82	52	Tio/Olo 5/5 once daily Olo 5 once daily	70	96	NR	NR	NR
Perng 2009	67	12	FP/SAL 500/50 twice daily Tio 18 once daily	73	94	61	1.21	NR
Hanania 2017	3267	52	Glyco/FM 18/9.6 twice daily Glyco 18 twice daily Tio 18 once daily FM 9.6 twice daily	63	56	54	NR	19.6
RADIATE 2016	812	52	IND/Glyco 110/50 once daily Tio 18 once daily	64	72	NR	NR	NR
Rheault 2016	1034	12	UMEC 62.5 once daily Glyco 50 once daily	64	69	48	1.34	13.2
Rossi 2014	581	26	FP/SAL 500/50 twice daily	66	69	36	1.54	9.7

Table 1. Study characteristics of included trials *(Continued)*

			IND 150 once daily					
SCO100470 2006	1050	24	FP/SAL 500/50 twice daily SAL 50 twice daily	64	78	43	1.67	NR
SCO40034 2005	125	12	FP/SAL 500/50 twice daily Tio 18 once daily	65	74	NR	1.37	NR
Singh 2014	1154	24	ACL/FM 400/12 twice daily ACL 400 twice daily FM 12 twice daily	63	67	47	1.41	NR
Singh 2015a	406	12	Tio/Olo 5/5 once daily Tio 5 once daily	65	59	52	1.31	14.5
Singh 2015b	405	12	Tio/Olo 5/5 once daily Tio 5 once daily	65	65	45	1.38	14.5
Singh 2015c	716	12	UMEC/VI 62.5/25 once daily FP/SAL 250/50 twice daily	62	72	59	1.44	10.8
Tashkin 2009	255	12	Tio 18 once daily + FM 12 twice daily Tio 18 once daily	64	66	47	NR	NR

Table 1. **Study characteristics of included trials** *(Continued)*

Tashkin 2012a&b	1340	26-52	MF/ FM 400/10 twice daily MF/ FM 200/10 twice daily FM 10 twice daily	60	75	49	1.21	8.9
To 2012	230	12	IND 150 once daily IND 300 once daily	67	97	34	1.24	15
Troosters 2016	152	12	Tio/Olo 5/5 once daily Tio 5 once daily	65	68	NR	NR	NR
Vincken 2014	447	12	IND/Glyco 110/50 once daily IND 150 once daily	64	81	42	1.46	19.5
Vogelmeier 2008	638	24	Tio 18 once daily + FM 10 twice daily Tio 18 once daily FM 10 twice daily	63	78	NR	1.50	10.8
Vogelmeier 2013a	522	26	IND/Glyco 110/50 once daily FP/ SAL 500/50 twice daily	63	71	48	1.45	20.4
Vogelmeier 2016	933	24	ACL/ FM 400/12 twice daily FP/ SAL 500/50 twice daily	63	65	NR	1.38	11.8

Table 1. Study characteristics of included trials *(Continued)*

Vogelmeier 2017	1080	12	IND/Glyco 110/50 once daily ICS/LABA free or fixed	65	64	49	NR	NR
Wise 2013	11392	120	Tio 5 once daily Tio 18 once daily	65	72	38	NR	NR
Yao 2014	375	26	IND 150 once daily IND 300 once daily	66	95	22	1.13	14.7
Zhong 2015	741	26	IND/Glyco 110/50 once daily FP/SAL 500/50 twice daily	65	91	26	1.08	24.1
ZuWallack 2014a&b	2267	12	Tio 18 once daily + Olo 5 once daily Tio 18 once daily	64	52	49	1.25	16

ACL: aclidinium; **BDP:** beclomethasone; **BUD:** budesonide; **FEV1:** forced expiratory volume in 1 second; **FF:** fluticasone furoate; **FM:** formoterol; **Glyco:** glycopyrrolate; **FP:** fluticasone propionate; **IND:** indacaterol; **MF:** mometasone furoate; **NR:** not reported; **Olo:** olodaterol; **SAL:** salmeterol; **Tio:** tiotropium; **UMEC:** umeclidinium; **VI:** vilanterol

Table 2. Study characteristics of treatment group pair-wise comparisons and clinical homogeneity assessment in moderate to severe exacerbations in the high-risk population

Comparison	**Comparisons**	**Number of participants**	**Mean age (years)**	**Male (%)**	**Current smoker (%)**	**Baseline FEV1 (L) prebronchodilator**	**Baseline FEV1 (L) postbronchodilator**	**Bronchial reversibility %**
LABA/ LAMA vs LABA/ICS	1	3372	65	76	40	NA	1.2	NA
LABA/ LAMA vs	1	2206	63	75	38	0.9	1.04	18.3

Table 2. Study characteristics of treatment group pair-wise comparisons and clinical homogeneity assessment in moderate to severe exacerbations in the high-risk population (*Continued*)

LAMA							
LABA/ LAMA vs LABA	0	0	NA	NA	NA	NA	NA	NA
LABA/ICS vs LAMA	2	1580	65	83	39	1.09	1.16	7
LABA/ICS vs LABA	10	9049	64	69	40	1.05	1.19	13.6
LAMA vs LABA	2	10,815	63	76	44	NA	1.32	NA

FEV1: forced expiratory volume in 1 second; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **NA:** not applicable

Table 3. Study characteristics of treatment group pair-wise comparisons and clinical homogeneity assessment in moderate to severe exacerbations in the low-risk population

Comparison	Comparisons	Number of participants	Mean age (years)	Male %	Current smoker %	Baseline FEV1 (L) pre-bronchodilator	Bronchial reversibility (%)
LABA/ LAMA vs LABA/ICS	6	4315	63	74	45	1.33	14.9
LABA/ LAMA vs LAMA	8	5192	63	71	47	1.32	14.7
LABA/ LAMA vs LABA	5	2488	64	68	44	1.36	17.5
LABA/ICS vs LAMA	1	623	63	65	52	1.35	13
LABA/ICS vs LABA	6	6689	64	74	44	1.27	11.1
LAMA vs LABA	5	4567	64	71	39	1.3	17.1

FEV1: forced expiratory volume in 1 second; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 4. Study characteristics of treatment group pair-wise comparisons and clinical homogeneity assessment in severe exacerbations in the high-risk population

Comparison	Comparisons	Number of participants	Mean age (years)	Male (%)	Current smoker (%)	Baseline FEV1 (L) postbronchodilator	Bronchial reversibility (%)
LABA/ LAMA vs LABA/ICS	1	3354	65	76	40	1	22.4
LABA/ LAMA vs LAMA	1	304	68	56	26	1.01	NA
LABA/ LAMA vs LABA	0	0	NA	NA	NA	NA	NA
LABA/ICS vs LAMA	2	1580	65	83	39	1.09	7
LABA/ICS vs LABA	5	4216	64	74	41	1.04	15.9
LAMA vs LABA	1	7376	63	76	48	NA	NA

FEV1: forced expiratory volume in 1 second; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **NA:** not applicable

Table 5. Study characteristics of treatment group pair-wise comparisons and clinical homogeneity assessment in severe exacerbations in the low-risk population

Comparison	Comparisons	Number of participants	Mean age (years)	Male (%)	Current smoker (%)	Baseline FEV1 (L) % prebronchodilator	Bronchial reversibility (%)	Baseline FEV1 (L) postbronchodilator
LABA/ LAMA vs LABA/ICS	6	2860	63	74	45	1.33	14.9	1.5
LABA/ LAMA vs LAMA	7	4973	63	72	41	1.33	15.1	1.49
LABA/ LAMA vs LABA	6	2898	64	67	45	1.35	18.3	1.55

Table 5. Study characteristics of treatment group pair-wise comparisons and clinical homogeneity assessment in severe exacerbations in the low-risk population *(Continued)*

LABA/ICS vs LAMA	1	623	63	65	52	1.35	13	1.48
LABA/ICS vs LABA	6	6482	64	74	44	1.27	11.1	1.32
LAMA vs LABA	4	3320	64	74	39	1.23	18.2	1.54

FEV1: forced expiratory volume in 1 second; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 6. Study characteristics of treatment group pair-wise comparisons and clinical homogeneity assessment in pneumonia in the low-risk population

Comparison	Comparisons	Number of participants	Mean age (years)	Male (%)	Current smoker (%)	Baseline FEV1 (L) prebronchodilator	Bronchial reversibility %
LABA/LAMA vs LABA/ICS	7	5395	64	72	46	1.33	14.9
LABA/LAMA vs LAMA	21	19,043	64	68	47	1.27	16.7
LABA/LAMA vs LABA	11	8556	64	65	43	1.30	15.8
LABA/ICS vs LAMA	4	2465	65	80	43	1.16	8.7
LABA/ICS vs LABA	16	15,992	64	72	41	1.14	11
LAMA vs LABA	12	22,351	63	70	43	1.34	16.8

FEV1: forced expiratory volume in 1 second; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 7. **Distribution of studies by individual treatment node in the high-risk population**

Class	Treatment node (drug, dose μg, dosing frequency)	Studies
LABA	Salmeterol 50 twice daily	Anzueto 2009; Calverley 2003 TRISTAN; Ferguson 2008; Kardos 2007; Ohar 2014; SCO40041 2008; Vogelmeier 2011
	Formoterol 9-12 twice daily	Calverley 2003; Calverley 2010; Ferguson 2017; Fukuchi 2013; Rennard 2009; Sharafkhaneh 2012; Szafranski 2003; Tashkin 2008; Wedzicha 2014
	Indacaterol 150 once daily	Bateman 2013; Decramer 2013
LAMA	Tiotripium 18 once daily	Aaron 2007; Asai 2013; Covelli 2016; Decramer 2013; Pepin 2014; Sarac 2016; Vogelmeier 2011; Wedzicha 2008; Wedzicha 2013
	Glycopyrrolate 50 once daily	Bateman 2013; Wedzicha 2013
LABA/ICS	Salmetrol/fluticasone 50/250 twice daily	Anzueto 2009; Ferguson 2008; Ohar 2014; SCO40041 2008; Wedzicha 2008
	Salmetrol/fluticasone 50/500 twice daily	Agusti 2014; Calverley 2003; Hagedorn 2013; Kardos 2007; Sarac 2016; Wedzicha 2016
	Formoterol/budesonide 9/160 twice daily	Rennard 2009; Sharafkhaneh 2012; Tashkin 2008
	Formoterol/budesonide 9/320 twice daily	Calverley 2003; Ferguson 2017; Fukuchi 2013; Rennard 2009; Sharafkhaneh 2012; Szafranski 2003; Tashkin 2008
	Formoterol/budesonide 12/400 twice daily DPI	Calverley 2010
	Formoterol/beclomethasone 12/200 twice daily	Calverley 2010; Wedzicha 2014
	Salmeterol 50 twice daily + fluticasone 250 twice daily[a]	COMBINE 2017
	Salmeterol 50 twice daily + fluticasone 500 twice daily[a]	Hagedorn 2013
	Vilanterol/fluticasone 25/100 once daily	Agusti 2014; Covelli 2016; Pepin 2014;
	Indacaterol 150 once daily + budesonide 400 twice daily [a]	COMBINE 2017
LABA/LAMA	Indacaterol/glycopyrrolate 27.5/15.6 twice daily	Ferguson 2016
	Indacaterol/glycopyrrolate 110/50 once daily	Asai 2013; Bateman 2013; Wedzicha 2013; Wedzicha 2016

Table 7. Distribution of studies by individual treatment node in the high-risk population *(Continued)*

	Salmeterol 50 twice daily + tiotropium 18 once daily[a]	Aaron 2007

[a] Free combination

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 8. Distribution of studies by individual treatment node in the low-risk population

Class	Treatment node (drug, dose μg, dosing frequency)	Studies
LABA	Salmeterol 50 twice daily	BI 205.137 2001; Briggs 2005; Brusasco 2003; Calverley 2007; Hanania 2003; Hoshino 2013; Jones 2011; Kornmann 2011; Mahler 2002; NCT00876694 2011; SCO100470 2006
	Formoterol 4.5 twice daily	Bogdan 2011
	Formoterol 9-12 twice daily	Bogdan 2011; Calverley 2010; Dahl 2010; Donohue 2016a; D'Urzo 2014; D'Urzo 2017; Hanania 2017; Jones 2011; Koch 2014; Martinez 2017a; Martinez 2017b; Singh 2014; Tashkin 2012a&b; Vogelmeier 2008
	Indacaterol 75 once daily	Ferguson 2016; Mahler 2016
	Indacaterol 150 once daily	Buhl 2011; Donohue 2010; Hoshino 2014; Jones 2011; Kornmann 2011; Rossi 2014; To 2012; Yao 2014; Vincken 2014
	Indacaterol 300 once daily	Dahl 2010; Donohue 2010; Jones 2011; NCT00876694 2011; To 2012; Yao 2014
	Olodaterol 5 once daily	Buhl 2015a&b; NCT01536262 2014; Koch 2014
LAMA	Tiotripium 18 once daily	BI 205.137 2001; Briggs 2005; Brusasco 2003; Buhl 2011; Cazzola 2007; Chapman 2014; COSMOS-J 2016; Covelli 2016; Decramer 2014a; Decramer 2014b; Donohue 2010; Fang 2008; Feldman 2016; GLOW4 2012; Hanania 2017; Hoshino 2013; Hoshino 2014; Kerwin 2012a; Kerwin 2017; Mahler 2012a; Mahler 2012b; Maleki-Yazdi 2014; Martinez 2017a; Perng 2009; RADIATE 2016; SCO40034 2005; Tashkin 2009; Vogelmeier 2008; Wise 2013; ZuWallack 2014a&b
	Tiotripium 5 once daily	Buhl 2015a; Buhl 2015b; Singh 2015a&b; Troosters 2016; Wise 2013
	Aclidinium 400 twice daily	D'Urzo 2014; D'Urzo 2017; Singh 2014

Table 8. Distribution of studies by individual treatment node in the low-risk population *(Continued)*

	Umeclidinium 62.5 once daily	Donohue 2013; Feldman 2016; Rheault 2016
	Glycopyrrolate 15.6 twice daily	Hanania 2017; Mahler 2015a; Mahler 2015b; Mahler 2016; Martinez 2017a; Martinez 2017b
	Glycopyrrolate 50 once daily	Chapman 2014; GLOW4 2012; Kerwin 2012a; Rheault 2016
LABA/ICS	Salmetrol/fluticasone 50/250 twice daily	COSMOS-J 2016; Donohue 2015a; Donohue 2015b; Dransfield 2014; Fang 2008; Hanania 2003; Hoshino 2013 ; Hoshino 2015; Koser 2010; Singh 2015d
	Salmetrol/fluticasone 50/500 twice daily	Calverley 2007; Cazzola 2007; Mahler 2002; Perng 2009; Rossi 2014; SCO100470 2006; SCO40034 2005; Vogelmeier 2013a; Vogelmeier 2016; Zhong 2015
	Salmetrol/fluticasone 42/230 (HFA) twice daily	Koser 2010
	Formoterol/budesonide 9/320 twice daily	Calverley 2010
	Formoterol/mometasone 200/10 twice daily	Tashkin 2012a&b
	Formoterol/mometasone 400/10 twice daily	Tashkin 2012a&b
	Vilanterol/fluticasone 25/100 once daily	Covelli 2016; Dransfield 2014
LABA/LAMA	Vilaterol/umeclidinium 25/62.5 once daily	Decramer 2014a; Decramer 2014b; Donohue 2013; Donohue 2015a; Donohue 2015b; Kalberg 2016; Kerwin 2017; Maleki-Yazdi 2014; Singh 2015d
	Formoterol/glycopyrrolate 9.6/18 twice daily	Hanania 2017; Martinez 2017a; Martinez 2017b
	Indacaterol/glycopyrrolate 27.5/15.6 twice daily	Ferguson 2016; Mahler 2015a; Mahler 2015b
	Indacaterol/glycopyrrolate 110/50 once daily	Buhl 2015c; RADIATE 2016; Vogelmeier 2013a; Vogelmeier 2017; Zhong 2015
	Olodaterol/tiotropium 5/5 once daily	Buhl 2015a&b; NCT01536262 2014; Singh 2015a&b; Troosters 2016
	Formterol/aclidinium 12/400 twice daily	Donohue 2016a; D'Urzo 2014; D'Urzo 2017; Singh 2014; Vogelmeier 2016
	Indacaterol 150 once daily + tiotropium 18 once daily[a]	Hoshino 2014; Hoshino 2015; Kalberg 2016; Mahler 2012a; Mahler 2012b
	Formoterol 10-12 twice daily + tiotropium 18 once daily [a]	Buhl 2015c; Tashkin 2009; Vogelmeier 2008

Table 8. Distribution of studies by individual treatment node in the low-risk population *(Continued)*

	Olodaterol 5 once daily + tiotropium 18 once daily[a]	ZuWallack 2014a&b
	Indacaterol 110 once daily + glycopyrrolate 50 once daily [a]	Vincken 2014

[a] Free combination

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 9. Relative effects: moderate to severe exacerbations in the high-risk population

Treatment comparison	Hazard ratios: random-effects	
	Median	95% CrI
LABA/LAMA v LABA/ICS	0.86	0.76 to 0.99
LABA/LAMA v LAMA	0.87	0.78 to 0.99
LABA/LAMA v LABA	0.70	0.61 to 0.80
LABA/ICS v LAMA	1.01	0.91 to 1.13
LABA/ICS v LABA	0.80	0.75 to 0.86
LAMA v LABA	0.80	0.71 to 0.88

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 10. Mean and median ranks: moderate to severe exacerbations in the high-risk population

Treatment group	Rank (from random-effects model)		
	Mean	Median	95% CrI
LABA/LAMA	1.0	1	1 to 2
LAMA	2.4	2	2 to 3
LABA/ICS	2.6	3	2 to 3
LABA	4.0	4	4 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 11. Relative effects: severe exacerbations in the high-risk population

Treatment comparison	Hazard ratios: fixed-effect		Hazard ratios: random-effects	
	Median	95% CrI	Median	95% CrI
LABA/LAMA v LABA/ ICS	0.78	0.64 to 0.93	0.78	0.62 to 0.98
LABA/LAMA v LAMA	0.89	0.71 to 1.11	0.91	0.73 to 1.13
LABA/LAMA v LABA	0.64	0.51 to 0.81	0.65	0.50 to 0.84
LABA/ICS v LAMA	1.15	0.97 to 1.36	1.16	0.94 to 1.41
LABA/ICS v LABA	0.83	0.71 to 0.97	0.83	0.69 to 1.00
LAMA v LABA	0.72	0.63 to 0.82	0.72	0.60 to 0.86

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 12. Mean and median ranks: severe exacerbations in the high-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	Median	95% CrI
LABA/LAMA	1.2	1	1 to 2
LAMA	1.9	2	1 to 3
LABA/ICS	3.0	3	2 to 3
LABA	4.0	4	4 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 13. Relative effects: St. George's Respiratory Questionnaire responders at 12 months in the high-risk population

Treatment comparison	Odds ratios: fixed-effect		Odds ratios: random-effects	
	Median	95% CrI	Median	95% CrI
LABA/LAMA v LABA/ ICS	1.21	1.07 to 1.36	1.19	0.83 to 1.71
LABA/LAMA v LAMA	1.36	1.18 to 1.58	1.34	0.93 to 1.88
LABA/LAMA v LABA	1.41	1.20 to 1.66	1.38	0.89 to 2.04

Table 13. Relative effects: St. George's Respiratory Questionnaire responders at 12 months in the high-risk population (*Continued*)

LABA/ICS v LAMA	1.13	0.98 to 1.30	1.12	0.81 to 1.54
LABA/ICS v LABA	1.17	1.02 to 1.34	1.15	0.87 to 1.49
LAMA v LABA	1.03	0.91 to 1.18	1.03	0.72 to 1.44

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 14. Mean and median ranks: St. George's Respiratory Questionnaire responders at 12 months in the high-risk population

Treatment group	**Rank (from fixed-effect model)**		
	Mean	**Median**	**95% CrI**
LABA/LAMA	1.0	1	1 to 1
LABA/ICS	2.1	2	2 to 3
LAMA	3.3	3	2 to 4
LABA	3.7	4	3 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 15. Relative effects: change from baseline in St. George's Respiratory Questionnaire score at 3 months in the high-risk population

Treatment comparison	**Mean differences - fixed effects**		**Mean differences - random effects**	
	Median	**95% CrI**	**Median**	**95% CrI**
LABA/LAMA v LABA/ICS	-1.39	(-2.37, -0.42)	-1.47	(-3.74, 0.45)
LABA/LAMA v LAMA	-3.31	(-4.67, -1.97)	-3.32	(-5.52, -1.12)
LABA/LAMA v LABA	-3.21	(-4.52, -1.92)	-3.21	(-5.63, -0.81)
LABA/ICS v LAMA	-1.92	(-3.11, -0.74)	-1.83	(-3.76, 0.35)
LABA/ICS v LABA	-1.82	(-2.86, -0.78)	-1.73	(-3.25, 0.05)
LAMA v LABA	0.1	(-0.76, 0.96)	0.1	(-1.86, 2.09)

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 16. Mean and median ranks: change from baseline in St. George's Respiratory Questionnaire score at 3 months in the high-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	Median	95% CrI
LABA/LAMA	1.0	1	1 to 1
LABA/ICS	2.0	2	2 to 2
LABA	3.4	3	3 to 4
LAMA	3.6	4	3 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 17. Relative effects: change from baseline in St. George's Respiratory Questionnaire score at 6 months in the high-risk population

Treatment comparison	Mean differences: fixed-effect		Mean differences: random-effects	
	Median	95% CrI	Median	95% CrI
LABA/LAMA v LABA/ ICS	−1.27	−2.26 to −0.29	−1.29	−3.03 to 0.46
LABA/LAMA v LAMA	−2.48	−3.72 to −1.24	−2.6	−4.52 to −0.75
LABA/LAMA v LABA	−2.88	−4.03 to −1.73	−2.9	−4.79 to −0.93
LABA/ICS v LAMA	−1.21	−2.16 to −0.25	−1.31	−2.90 to 0.17
LABA/ICS v LABA	−1.60	−2.27 to −0.93	−1.61	−2.61 to −0.54
LAMA v LABA	−0.39	−1.27 to 0.47	−0.3	−1.74 to 1.34

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 18. Mean and median ranks: change from baseline in St. George's Respiratory Questionnaire score at 6 months in the high-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	Median	95% CrI
LABA/LAMA	1.0	1	1 to 1
LABA/ICS	2.0	2	2 to 2

Table 18. Mean and median ranks: change from baseline in St. George's Respiratory Questionnaire score at 6 months in the high-risk population *(Continued)*

LAMA	3.2	3	3 to 4
LABA	3.8	4	3 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 19. Relative effects: change from baseline in St. George's Respiratory Questionnaire score at 12 months in the high-risk population

Treatment comparison	Mean differences: fixed-effect		Mean differences: random-effects	
	Median	**95% CrI**	**Median**	**95% CrI**
LABA/LAMA v LABA/ICS	−0.52	−1.42 to 0.36	−0.69	−2.46 to 0.87
LABA/LAMA v LAMA	−1.12	−1.88 to −0.37	−1.49	−3.16 to −0.20
LABA/LAMA v LABA	−2.10	−3.08 to −1.13	−2.31	−4.17 to −0.64
LABA/ICS v LAMA	−0.59	−1.48 to 0.29	−0.79	−2.40 to 0.65
LABA/ICS v LABA	−1.57	−2.23 to −0.92	−1.61	−2.52 to −0.69
LAMA v LABA	−0.98	−1.86 to −0.08	−0.82	−2.29 to 0.84

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 20. Mean and median ranks: change from baseline in St. George's Respiratory Questionnaire score at 12 months in the high-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	**Median**	**95% CrI**
LABA/LAMA	1.1	1	1 to 2
LABA/ICS	2.0	2	1 to 3
LAMA	2.9	3	2 to 3
LABA	4.0	4	4 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 21. Relative effects: change from baseline in forced expiratory volume in 1 second at 3 months in the high-risk population

Treatment comparison	Mean differences: fixed-effect		Mean differences: random-effects	
	Median	95% CrI	Median	95% CrI
LABA/LAMA v LABA/ICS	0.07	0.05 to 0.09	0.07	0.03 to 0.10
LABA/LAMA v LAMA	0.07	0.05 to 0.10	0.07	0.04 to 0.11
LABA/LAMA v LABA	0.12	0.10 to 0.15	0.12	0.07 to 0.15
LABA/ICS v LAMA	0	−0.02 to 0.02	0.01	−0.02 to 0.04
LABA/ICS v LABA	0.05	0.04 to 0.07	0.05	0.03 to 0.07
LAMA v LABA	0.05	0.02 to 0.07	0.04	0.00 to 0.08

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 22. Mean and median ranks: change from baseline in forced expiratory volume in 1 second at 3 months in the high-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	Median	95% CrI
LABA/LAMA	1.0	1	1 to 1
LABA/ICS	2.4	2	2 to 3
LAMA	2.6	3	2 to 3
LABA	4.0	4	4 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 23. Relative effects: change from baseline in forced expiratory volume in 1 second at 6 months in the high-risk population

Treatment comparison	Mean differences: fixed-effect		Mean differences: random-effects	
	Median	95% CrI	Median	95% CrI
LABA/LAMA v LABA/ICS	0.08	0.06 to 0.10	0.08	0.04 to 0.12
LABA/LAMA v LAMA	0.07	0.04 to 0.09	0.07	0.02 to 0.11

Table 23. Relative effects: change from baseline in forced expiratory volume in 1 second at 6 months in the high-risk population (*Continued*)

LABA/LAMA v LABA	0.13	0.10 to 0.15	0.13	0.09 to 0.18
LABA/ICS v LAMA	−0.02	−0.04 to 0.01	−0.02	−0.06 to 0.03
LABA/ICS v LABA	0.04	0.03 to 0.06	0.05	0.03 to 0.08
LAMA v LABA	0.06	0.03 to 0.08	0.06	0.02 to 0.11

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 24. Mean and median ranks: change from baseline in forced expiratory volume in 1 second at 6 months in the high-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	**Median**	**95% CrI**
LABA/LAMA	1.0	1	1 to 1
LAMA	2.1	2	2 to 3
LABA/ICS	2.9	3	2 to 3
LABA	4.0	4	4 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 25. Relative effects: change from baseline in forced expiratory volume in 1 second at 12 months in the high-risk population

Treatment comparison	Mean differences: fixed-effect		Mean differences: random-effects	
	Median	**95% CrI**	**Median**	**95% CrI**
LABA/LAMA v LABA/ICS	0.07	0.05 to 0.09	0.07	0.04 to 0.10
LABA/LAMA v LAMA	0.04	0.01 to 0.07	0.04	0.00 to 0.08
LABA/LAMA v LABA	0.11	0.09 to 0.14	0.12	0.08 to 0.16
LABA/ICS v LAMA	−0.03	−0.06 to 0.00	−0.03	−0.07 to 0.01
LABA/ICS v LABA	0.05	0.03 to 0.06	0.05	0.03 to 0.07
LAMA v LABA	0.07	0.04 to 0.11	0.08	0.04 to 0.12

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 26. Mean and median ranks: change from baseline in forced expiratory volume in 1 second at 12 months in the high-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	Median	95% CrI
LABA/LAMA	1.0	1	1 to 1
LAMA	2.0	2	2 to 2
LABA/ICS	3.0	3	3 to 3
LABA	4.0	4	4 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 27. Relative effects: mortality in the high-risk population

Treatment comparison	Odds ratios: fixed-effect		Odds ratios: random-effects	
	Median	95% CrI	Median	95% CrI
LABA/LAMA v LABA/ICS	1.12	0.75 to 1.68	1.15	0.70 to 1.95
LABA/LAMA v LAMA	0.98	0.66 to 1.42	0.99	0.62 to 1.60
LABA/LAMA v LABA	0.97	0.63 to 1.46	1.04	0.63 to 1.86
LABA/ICS v LAMA	0.87	0.65 to 1.16	0.86	0.58 to 1.26
LABA/ICS v LABA	0.86	0.66 to 1.11	0.91	0.68 to 1.23
LAMA v LABA	0.99	0.77 to 1.27	1.05	0.75 to 1.59

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 28. Mean and median ranks: mortality in the high-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	Median	95% CrI
LABA/ICS	1.6	1	1 to 4

Table 28. Mean and median ranks: mortality in the high-risk population (*Continued*)

LABA/LAMA	2.6	3	1 to 4
LAMA	2.8	3	1 to 4
LABA	3.0	3	1 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 29. Relative effects: serious adverse events in the high-risk population

Treatment comparison	**Odds ratios: fixed-effect**		**Odds ratios: random-effects**	
	Median	**95% CrI**	**Median**	**95% CrI**
Total SAEs				
LABA/LAMA vs LABA/ICS	0.89	0.77 to 1.02	0.89	0.74 to 1.06
LABA/LAMA vs LAMA	1.01	0.87 to 1.17	1.01	0.83 to 1.21
LABA/LAMA vs LABA	0.89	0.77 to 1.04	0.89	0.73 to 1.08
LABA/ICS vs LAMA	1.14	1.02 to 1.27	1.13	0.99 to 1.31
LABA/ICS vs LABA	1.01	0.92 to 1.10	1.01	0.91 to 1.12
LAMA vs LABA	0.88	0.81 to 0.97	0.89	0.78 to 1.01
COPD SAEs				
LABA/LAMA vs LABA/ICS	0.87	0.73 to 1.04	0.87	0.71 to 1.09
LABA/LAMA vs LAMA	1.07	0.89 to 1.28	1.07	0.85 to 1.34
LABA/LAMA vs LABA	0.82	0.68 to 1.00	0.83	0.65 to 1.05
LABA/ICS vs LAMA	1.22	1.05 to 1.42	1.22	1.02 to 1.46
LABA/ICS vs LABA	0.95	0.83 to 1.08	0.94	0.81 to 1.09
LAMA vs LABA	0.77	0.68 to 0.87	0.77	0.66 to 0.91
CARDIAC SAEs				

Table 29. Relative effects: serious adverse events in the high-risk population (*Continued*)

LABA/LAMA vs LABA/ICS	0.91	0.66 to 1.25	0.70	0.03 to 5.88
LABA/LAMA vs LAMA	0.75	0.54 to 1.03	0.69	0.02 to 25.46
LABA/LAMA vs LABA	0.85	0.60 to 1.19	0.83	0.06 to 9.24
LABA/ICS vs LAMA	0.83	0.63 to 1.08	1.08	0.06 to 23.81
LABA/ICS vs LABA	0.93	0.75 to 1.16	1.27	0.37 to 5.97
LAMA vs LABA	1.13	0.89 to 1.42	1.13	0.06 to 21.22

COPD: chronic obstructive pulmonary disease; **CrI:** credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist;**SAE:** serious adverse event

Table 30. Certainty of evidence: serious adverse events in the high-risk population

Treatment comparison	Total SAEs	COPD SAEs	Cardiac SAEs
LABA/LAMA vs LABA/ICS	Moderate	Moderate	Moderate
LABA/LAMA vs LAMA	Moderate	Moderate	Moderate
LABA/LAMA vs LABA	NA	NA	NA
LABA/ICS vs LAMA	Moderate	Moderate	Moderate
LABA/ICS vs LABA	Moderate	Moderate	Moderate
LAMA vs LABA	High	High	Low

COPD: chronic obstructive pulmonary disease; **CrI:** credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist;**NA:** not applicable; **SAE:** serious adverse event

Table 31. Relative effects: dropouts due to adverse events in the high-risk population

Treatment comparison	Odds ratios: fixed-effect		Odds ratios: random-effects	
	Median	**95% CrI**	**Median**	**95% CrI**
LABA/LAMA vs LABA/ICS	0.93	0.76 to 1.14	0.93	0.73 to 1.19
LABA/LAMA vs LAMA	0.94	0.76 to 1.17	0.95	0.74 to 1.21

Table 31. Relative effects: dropouts due to adverse events in the high-risk population (*Continued)*

LABA/LAMA vs LABA	0.83	0.67 to 1.03	0.83	0.65 to 1.07
LABA/ICS vs LAMA	1.01	0.87 to 1.19	1.02	0.85 to 1.22
LABA/ICS vs LABA	0.89	0.79 to 1.01	0.89	0.79 to 1.01
LAMA vs LABA	0.88	0.77 to 1.01	0.88	0.75 to 1.03

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 32. Mean and median ranks: dropouts due to adverse events in the high-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	**Median**	**95% CrI**
LABA/LAMA	1.6	1	1 to 4
LAMA	2.2	2	1 to 4
LABA/ICS	2.4	2	1 to 4
LABA	3.9	4	3 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 33. Relative effects: pneumonia in the high-risk population

Treatment comparison	Odds ratios: fixed-effect		Odds ratios: random-effects	
	Median	**95% CrI**	**Median**	**95% CrI**
LABA/LAMA vs LABA/ICS	0.59	0.41 to 0.83	0.59	0.35 to 1.01
LABA/LAMA vs LAMA	1.05	0.72 to 1.5	1.05	0.63 to 1.81
LABA/LAMA vs LABA	0.88	0.60 to 1.29	0.87	0.49 to 1.52
LABA/ICS vs LAMA	1.78	1.33 to 2.39	1.79	1.19 to 2.76
LABA/ICS vs LABA	1.50	1.17 to 1.92	1.48	1.10 to 1.98
LAMA vs LABA	0.84	0.65 to 1.09	0.83	0.54 to 1.21

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 34. Mean and median ranks: pneumonia in the high-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	Median	95% CrI
LAMA	1.5	1	1 to 3
LABA/LAMA	1.9	2	1 to 3
LABA	2.6	3	1 to 3
LABA/ICS	4.0	4	4 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 35. Relative effects: moderate to severe exacerbations in the low-risk population

Treatment comparison	Hazard ratios: fixed-effect		Hazard ratios: random-effects	
	Median	95% CrI	Median	95% CrI
LABA/LAMA vs LABA/ICS	0.87	0.75 to 1.01	0.89	0.78 to 1.04
LABA/LAMA vs LAMA	0.90	0.76 to 1.06	0.88	0.76 to 1.01
LABA/LAMA vs LABA	0.78	0.67 to 0.90	0.78	0.69 to 0.89
LABA/ICS vs LAMA	1.03	0.91 to 1.17	0.98	0.83 to 1.14
LABA/ICS vs LABA	0.89	0.84 to 0.96	0.88	0.78 to 0.96
LAMA vs LABA	0.87	0.78 to 0.97	0.89	0.78 to 1.01

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 36. Mean and median group ranks: moderate to severe exacerbations in the low-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	Median	95% CrI
LABA/LAMA	1.1	1	1 to 2
LAMA	2.2	2	1 to 3
LABA/ICS	2.6	3	2 to 3

Table 36. Mean and median group ranks: moderate to severe exacerbations in the low-risk population *(Continued)*

LABA	4.0	4	4 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 37. Study characteristics of treatment group pair-wise comparisons and transitivity assessment in moderate to severe exacerbations in the low-risk population

Comparison	Comparisons	Number of participants	Mean age (years)	Male (%)	Baseline FEV1 (L) prebronchodilator	Current smoker (%)	Bronchial reversibility (%)
LABA/LAMA vs LABA/ICS	6	4315	63	74	45	1.33	14.9
LABA/LAMA vs LAMA	8	5192	63	71	47	1.32	14.7
LABA/LAMA vs LABA	5	2488	64	68	44	1.36	17.5
LABA/ICS vs LAMA	1	623	63	65	52	1.35	13
LABA/ICS vs LABA	6	6689	64	74	44	1.27	11.1
LAMA vs LABA	5	4567	64	71	39	1.3	17.1

CrI: credible interval; **FEV1:** forced expiratory volume in 1 second; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 38. Relative effects: severe exacerbations in the low-risk population

Treatment comparison	Hazard ratios: fixed-effect		Hazard ratios: random-effects	
	Median	95% CrI	Median	95% CrI
LABA/LAMA vs LABA/ICS	0.71	0.50 to 1.02	0.71	0.47 to 1.08
LABA/LAMA vs LAMA	0.88	0.62 to 1.24	0.90	0.60 to 1.31

Table 38. Relative effects: severe exacerbations in the low-risk population *(Continued)*

LABA/LAMA vs LABA	0.73	0.51 to 1.03	0.72	0.48 to 1.02
LABA/ICS vs LAMA	1.23	0.96 to 1.57	1.25	0.86 to 1.85
LABA/ICS vs LABA	1.02	0.89 to 1.17	1.01	0.72 to 1.28
LAMA vs LABA	0.83	0.67 to 1.03	0.80	0.56 to 1.05

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 39. Mean and median ranks: severe exacerbations in the low-risk population

Treatment group	**Rank (from fixed-effect model)**		
	Mean	**Median**	**95% CrI**
LABA/LAMA	1.3	1	1 to 3
LAMA	1.9	2	1 to 3
LABA	3.3	3	2 to 4
LABA/ICS	3.5	4	2 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 40. Relative effects: St. George's Respiratory Questionnaire responders at 3 months in the low-risk population

Treatment comparison	**Odds ratios: fixed-effect**		**Odds ratios: random-effects**	
	Median	**95% CrI**	**Median**	**95% CrI**
LABA/LAMA vs LABA/ICS	1.07	0.94 to 1.23	1.07	0.93 to 1.23
LABA/LAMA vs LAMA	1.33	1.19 to 1.48	1.32	1.18 to 1.49
LABA/LAMA vs LABA	0.96	0.81 to 1.15	0.96	0.79 to 1.17
LABA/ICS vs LAMA	1.24	1.07 to 1.43	1.24	1.06 to 1.45
LABA/ICS vs LABA	0.9	0.76 to 1.06	0.9	0.75 to 1.08
LAMA vs LABA	0.73	0.62 to 0.85	0.72	0.60 to 0.87

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 41. Mean and median ranks: St. George's Respiratory Questionnaire responders at 3 months in the low-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	Median	95% CrI
LABA	1.4	1	1 to 3
LABA/LAMA	1.8	2	1 to 3
LABA/ICS	2.8	3	1 to 3
LAMA	4.0	4	4 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 42. Relative effects: SGRQ responders at 6 months in the low-risk population

Treatment comparison	Odds ratios: random-effects	
	Median	95% CrI
LABA/LAMA vs LABA/ICS	1.22	0.99 to 1.51
LABA/LAMA vs LAMA	1.26	1.10 to 1.42
LABA/LAMA vs LABA	1.28	1.11 to 1.47
LABA/ICS vs LAMA	1.03	0.83 to 1.27
LABA/ICS vs LABA	1.05	0.87 to 1.25
LAMA vs LABA	1.02	0.90 to 1.16

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 43. Mean and median ranks: St. George's Respiratory Questionnaire responders at 6 months in the low-risk population

Treatment group	Rank (from random-effects model)		
	Mean	Median	95% CrI
LABA/LAMA	1.0	1	1 to 2
LABA/ICS	2.7	2	1 to 4
LAMA	3.0	3	2 to 4
LABA	3.3	3	2 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 44. Change from baseline in St. George's Respiratory Questionnaire score at 3 months in the low-risk population

Treatment comparison	Mean differences: fixed-effect		Mean differences: random-effects	
	Median	95% CrI	Median	95% CrI
LABA/LAMA vs LABA/ICS	0.04	−0.79 to 0.88	0.04	−0.84 to 0.88
LABA/LAMA vs LAMA	−1.64	−2.2 to −1.08	−1.64	−2.25 to −1.05
LABA/LAMA vs LABA	−0.63	−1.86 to 0.6	−0.62	−1.95 to 0.65
LABA/ICS vs LAMA	−1.68	−2.59 to −0.78	−1.68	−2.6 to −0.74
LABA/ICS vs LABA	−0.67	−1.88 to 0.54	−0.67	−1.92 to 0.57
LAMA vs LABA	1.01	−0.2 to 2.22	1.02	−0.26 to 2.27

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 45. Mean and median ranks: change from baseline in St. George's Respiratory Questionnaire score at 3 months in the low-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	Median	95% CrI
LABA/ICS	1.6	2	1 to 3
LABA/LAMA	1.7	2	1 to 3
LABA	2.8	3	1 to 4
LAMA	3.9	4	3 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 46. Relative effects: change from baseline in SGRQ score at 6 months in the low-risk population

Treatment comparison	Mean differences: fixed-effect		Mean differences: random-effects	
	Median	95% CrI	Median	95% CrI

Table 46. Relative effects: change from baseline in SGRQ score at 6 months in the low-risk population (*Continued)*

LABA/LAMA vs LABA/ICS	−0.22	−1.28 to 0.82	−0.3	−1.50 to 0.93
LABA/LAMA vs LAMA	−1.18	−1.80 to −0.56	−1.17	−1.91 to −0.48
LABA/LAMA vs LABA	−1.36	−2.12 to −0.6	−1.4	−2.24 to −0.51
LABA/ICS vs LAMA	−0.96	−1.98 to 0.09	−0.89	−2.08 to 0.33
LABA/ICS vs LABA	−1.14	−1.90 to −0.37	−1.11	−2.01 to −0.16
LAMA vs LABA	−0.18	−0.91 to 0.55	−0.21	−1.05 to 0.61

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 47. Mean and median ranks: St. George's Respiratory Questionnaire at 6 months in the low-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	**Median**	**95% CrI**
LABA/LAMA	1.3	1	1 to 2
LABA/ICS	1.7	2	1 to 3
LAMA	3.3	3	2 to 4
LABA	3.7	4	3 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 48. Relative effects: change from baseline in St. George's Respiratory Questionnaire score at 12 months in the low-risk population

Treatment comparison	Mean differences: fixed-effect		Mean differences: random-effects	
	Median	**95% CrI**	**Median**	**95% CrI**
LABA/LAMA vs LABA/ICS	0.97	−0.48 to 2.42	1.05	−1.78 to 3.98
LABA/LAMA vs LAMA	−0.89	−1.66 to −0.11	−0.8	−2.05 to 0.62
LABA/LAMA vs LABA	−0.72	−1.64 to 0.20	−0.65	−2.29 to 1.11

Table 48. Relative effects: change from baseline in St. George's Respiratory Questionnaire score at 12 months in the low-risk population (*Continued*)

LABA/ICS vs LAMA	−1.85	−3.28 to −0.43	−1.86	−4.63 to 1.02
LABA/ICS vs LABA	−1.69	−2.81 to −0.57	−1.71	−4.02 to 0.65
LAMA vs LABA	0.16	−0.72 to 1.04	0.13	−1.48 to 1.74

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 49. Mean and median ranks: change from baseline in St. George's Respiratory Questionnaire score at 12 months in the low-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	**Median**	**95% CrI**
LABA/ICS	1.1	1	1 to 2
LABA/LAMA	2.0	2	1 to 3
LABA	3.3	3	2 to 4
LAMA	3.6	4	3 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 50. Relative effects: Transition Dyspnea Index at 3 months in the low-risk population

Treatment comparison	Mean differences: random-effects (fixed-class)		Mean differences: fixed-effect (random-class)	
	Median	**95% CrI**	**Median**	**95% CrI**
LABA/LAMA vs LABA/ICS	0.35	0.12 to 0.56	0.48	0.09 to 0.99
LABA/LAMA vs LAMA	0.54	0.36 to 0.73	0.55	0.22 to 0.90
LABA/LAMA vs LABA	0.44	0.20 to 0.67	0.47	0.09 to 0.85
LABA/ICS vs LAMA	0.19	−0.07 to 0.47	0.06	−0.43 to 0.48
LABA/ICS vs LABA	0.09	−0.18 to 0.36	−0.02	−0.48 to 0.37
LAMA vs LABA	−0.1	−0.36 to 0.14	−0.08	−0.46 to 0.28

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 51. Median and mean ranks: Transition Dyspnea Index at 3 months in the low-risk population

Treatment group	Rank (from random-effects, fixed-class)		
	Mean	Median	95% CrI
LABA/LAMA	1.0	1	1 to 1
LABA/ICS	2.3	2	2 to 4
LABA	3.0	3	2 to 4
LAMA	3.7	4	2 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 52. Relative effects: Transition Dyspnea Index at 6 months in the low-risk population

Treatment comparison	Mean differences: random-effects (fixed-class)		Mean differences: fixed-effect (random-class)	
	Median	95% CrI	Median	95% CrI
LABA/LAMA vs LABA/ICS	0.15	−0.10 to 0.4	0.14	−0.14 to 0.41
LABA/LAMA vs LAMA	0.33	0.18 to 0.47	0.32	0.15 to 0.48
LABA/LAMA vs LABA	0.37	0.21 to 0.52	0.36	0.18 to 0.55
LABA/ICS vs LAMA	0.18	−0.09 to 0.45	0.18	−0.12 to 0.50
LABA/ICS vs LABA	0.22	−0.02 to 0.46	0.22	−0.04 to 0.50
LAMA vs LABA	0.04	−0.12 to 0.21	0.04	−0.15 to 0.24

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 53. Mean and median ranks: Transition Dyspnea Index at 6 months in the low-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	Median	95% CrI
LABA/LAMA	1.1	1	1 to 2
LABA/ICS	2.0	2	1 to 4

Table 53. Mean and median ranks: Transition Dyspnea Index at 6 months in the low-risk population *(Continued)*

LAMA	3.2	3	2 to 4
LABA	3.6	4	3 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 54. Relative effects: Transition Dyspnea Index at 12 months in the low-risk population

Treatment comparison	Mean differences: random-effects (fixed-class)		Mean differences: fixed-effect (random-class)	
	Median	**95% CrI**	**Median**	**95% CrI**
LABA/LAMA vs LAMA	0.20	0.09 to 0.32	0.22	−0.05 to 0.51
LABA/LAMA vs LABA	0.30	0.17 to 0.42	0.37	0.11 to 0.71
LAMA vs LABA	0.09	−0.02 to 0.21	0.15	−0.10 to 0.46

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 55. Mean and median ranks: Transition Dyspnea Index at 12 months in the low-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	**Median**	**95% CrI**
LABA/LAMA	1.00	1	1 to 1
LAMA	2.06	2	2 to 3
LABA	2.94	3	2 to 3

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 56. Relative effects: change from baseline in forced expiratory volume in 1 second at 3 months in the low-risk population

Treatment comparison	Mean differences: random-effects	
	Median	**95% CrI**
LABA/LAMA vs LABA/ICS	0.05	0.03 to 0.07
LABA/LAMA vs LAMA	0.08	0.06 to 0.09

Table 56. Relative effects: change from baseline in forced expiratory volume in 1 second at 3 months in the low-risk population (*Continued*)

LABA/LAMA vs LABA	0.09	0.07 to 0.11
LABA/ICS vs LAMA	0.02	0.00 to 0.04
LABA/ICS vs LABA	0.03	0.01 to 0.05
LAMA vs LABA	0.01	−0.01 to 0.03

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 57. Mean and median ranks: change from baseline in forced expiratory volume in 1 second at 3 months in the low-risk population

Treatment group	Rank (from random-effects model)		
	Mean	**Median**	**95% CrI**
LABA/LAMA	1.0	1	1 to 1
LABA/ICS	2.0	2	2 to 2
LAMA	3.2	3	3 to 4
LABA	3.8	4	3 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 58. Relative effects: change from baseline in forced expiratory volume in 1 second at 6 months in the low-risk population

Treatment comparison	Mean differences: random-effects		Mean differences: fixed-effect (random-class)	
	Median	**95% CrI**	**Median**	**95% CrI**
LABA/LAMA vs LABA/ICS	0.05	0.03 to 0.08	0.05	−0.01 to 0.11
LABA/LAMA vs LAMA	0.06	0.05 to 0.08	0.06	0.02 to 0.09
LABA/LAMA vs LABA	0.08	0.06 to 0.09	0.08	0.04 to 0.11
LABA/ICS vs LAMA	0.01	−0.02 to 0.04	0.01	−0.05 to 0.07
LABA/ICS vs LABA	0.02	−0.01 to 0.05	0.03	−0.02 to 0.08
LAMA vs LABA	0.01	0.00 to 0.03	0.02	−0.01 to 0.05

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 59. Mean and median ranks: change from baseline in forced expiratory volume in 1 second at 6 months in the low-risk population

Treatment group	Rank (from random-effects to fixed-class)		
	Mean	Median	95% CrI
LABA/LAMA	1.0	1	1 to 1
LABA/ICS	2.3	2	2 to 4
LAMA	2.7	3	2 to 4
LABA	3.9	4	3 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 60. Relative effects: change from baseline in forced expiratory volume in 1 second at 12 months in the low-risk population

Treatment comparison	Mean differences− fixed effects		Mean differences: random-effects	
	Median	95% CrI	Median	95% CrI
LABA/LAMA vs LAMA	0.06	−0.01 to 0.12	0.06	0.04 to 0.08
LABA/LAMA vs LABA	0.08	0.02 to 0.14	0.08	0.06 to 0.10
LAMA vs LABA	0.02	0.00 to 0.06	0.02	0.00 to 0.04

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 61. Mean and median ranks: change from baseline in forced expiratory volume in 1 second at 12 months in the low-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	Median	95% CrI
LABA/LAMA	1.1	1	1 to 2
LAMA	2.0	2	1 to 3
LABA	3.0	3	2 to 3

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 62. Intervention effects: change from baseline in forced expiratory volume in 1 second at 12 months in the low-risk population

Intervention	Median	95% CrI
Formoterol 9−12 twice daily	**Reference**	
Indacaterol 75 once daily	0.002	−0.029 to 0.048
Olodaterol 5 once daily	0.001	−0.018 to 0.022
Tiotripium 18 once daily	0.034	0.016 to 0.054
Tiotripium 5 once daily	0.031	0.009 to 0.056
Aclidinium 400 twice daily	0.027	−0.002 to 0.060
Glycopyrronium 15.6 twice daily	0.010	−0.006 to 0.027
Glycopyrronium 50 once daily	0.022	−0.022 to 0.062
Formoterol/glycopyrronium 9.6/18 twice daily	0.066	0.050 to 0.081
Indacaterol/glycopyrronium 27.5/15.6 twice daily	0.083	0.034 to 0.137
Indacaterol/glycopyrronium 110/50 once daily	0.128	0.091 to 0.165
Olodaterol/tiotropium 5/5 once daily	0.089	0.066 to 0.114
Formterol/aclidinium 12/400 twice daily	0.044	0.005 to 0.081

CrI: credible interval

Table 63. Relative effects: mortality in the low-risk population

Treatment comparison	Odds ratios: fixed-effect		Odds ratios: random-effects	
	Median	95% CrI	Median	95% CrI
LABA/LAMA vs LABA/ICS	1.25	0.79 to 2.00	1.27	0.69 to 2.30
LABA/LAMA vs LAMA	0.91	0.63 to 1.32	0.90	0.59 to 1.34
LABA/LAMA vs LABA	1.16	0.75 to 1.81	1.19	0.73 to 1.98

Table 63. Relative effects: mortality in the low-risk population (*Continued*)

LABA/ICS vs LAMA	0.73	0.45 to 1.16	0.72	0.37 to 1.30
LABA/ICS vs LABA	0.93	0.76 to 1.14	0.94	0.59 to 1.52
LAMA vs LABA	1.28	0.83 to 1.98	1.31	0.82 to 2.22

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 64. Mean and median ranks: mortality in the low-risk population

Treatment group	**Rank (from fixed-effect model)**		
	Mean	**Median**	**95% CrI**
LABA/ICS	1.5	1	1 to 4
LABA	2.1	2	1 to 4
LABA/LAMA	3.0	3	1 to 4
LAMA	3.5	4	1 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 65. Relative effects: serious adverse events in the low-risk population

Treatment comparison	**Odds ratios: fixed-effect**		**Odds ratios: random-effects**	
	Median	**95% CrI**	**Median**	**95% CrI**
Total SAEs				
LABA/LAMA vs LABA/ICS	0.91	0.78 to 1.05	0.91	0.77 to 1.06
LABA/LAMA vs LAMA	1.03	0.93 to 1.15	1.03	0.92 to 1.16
LABA/LAMA vs LABA	1.02	0.91 to 1.15	1.02	0.90 to 1.16
LABA/ICS vs LAMA	1.14	0.98 to 1.32	1.14	0.97 to 1.35
LABA/ICS vs LABA	1.13	1.01 to 1.27	1.13	0.99 to 1.29
LAMA vs LABA	0.99	0.88 to 1.11	0.99	0.87 to 1.12
COPD SAEs				

Table 65. Relative effects: serious adverse events in the low-risk population (*Continued*)

LABA/LAMA vs LABA/ICS	0.96	0.75 to 1.22	0.92	0.67 to 1.26
LABA/LAMA vs LAMA	0.99	0.82 to 1.19	0.98	0.78 to 1.21
LABA/LAMA vs LABA	0.92	0.75 to 1.13	0.89	0.68 to 1.13
LABA/ICS vs LAMA	1.04	0.81 to 1.32	1.06	0.77 to 1.48
LABA/ICS vs LABA	0.96	0.82 to 1.13	0.96	0.73 to 1.25
LAMA vs LABA	0.93	0.76 to 1.14	0.9	0.71 to 1.14
Cardiac SAEs				
LABA/LAMA vs LABA/ICS	1.28	0.91 to 1.81	1.24	0.81 to 1.83
LABA/LAMA vs LAMA	1.05	0.80 to 1.36	1.04	0.77 to 1.37
LABA/LAMA vs LABA	1.24	0.92 to 1.68	1.24	0.89 to 1.71
LABA/ICS vs LAMA	0.82	0.58 to 1.15	0.84	0.56 to 1.27
LABA/ICS vs LABA	0.97	0.79 to 1.19	0.99	0.74 to 1.41
LAMA vs LABA	1.19	0.89 to 1.59	1.19	0.88 to 1.64

COPD: chronic obstructive pulmonary disease; **CrI:** credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **SAE:** serious adverse event

Table 66. Certainty of evidence: serious adverse events in the low-risk population

Treatment comparison	Total SAEs	COPD SAEs	Cardiac SAEs
LABA/LAMA vs LABA/ICS	Moderate	Low	Moderate
LABA/LAMA vs LAMA	High	High	Moderate
LABA/LAMA vs LABA	High	Moderate	Moderate
LABA/ICS vs LAMA	Moderate	Moderate	Moderate
LABA/ICS vs LABA	Low	High	High

Table 66. Certainty of evidence: serious adverse events in the low-risk population (*Continued*)

LAMA vs LABA	High	Low	Moderate

COPD: chronic obstructive pulmonary disease; **CrI:** credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **SAE:** serious adverse event

Table 67. Relative effects: dropouts due to adverse events in the low-risk population

Treatment comparison	Odds ratios: fixed-effect		Odds ratios: random-effects	
	Median	**95% CrI**	**Median**	**95% CrI**
LABA/LAMA vs LABA/ICS	0.99	0.83 to 1.18	0.99	0.82 to 1.2
LABA/LAMA vs LAMA	1.09	0.95 to 1.26	1.09	0.94 to 1.28
LABA/LAMA vs LABA	0.91	0.78 to 1.06	0.91	0.77 to 1.07
LABA/ICS vs LAMA	1.11	0.92 to 1.33	1.11	0.89 to 1.37
LABA/ICS vs LABA	0.92	0.8 to 1.06	0.92	0.77 to 1.09
LAMA vs LABA	0.84	0.72 to 0.97	0.83	0.7 to 0.98

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 68. Mean and median ranks: dropouts due to adverse events in the low-risk population

Treatment group	Rank (from fixed-effect model)		
	Mean	**Median**	**95% CrI**
LAMA	1.3	1	1 to 3
LABA/ICS	2.5	3	1 to 4
LABA/LAMA	2.5	2	1 to 4
LABA	3.7	4	2 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 69. Relative effects: pneumonia in the low-risk population

Treatment comparison	Odds ratios: fixed-effect		Odds ratios: random-effects	
	Median	95% CrI	Median	95% CrI
LABA/LAMA vs LABA/ICS	0.67	0.44 to 1.01	0.61	0.34 to 1.01
LABA/LAMA vs LAMA	1.24	0.87 to 1.77	1.23	0.82 to 1.84
LABA/LAMA vs LABA	1.21	0.83 to 1.77	1.18	0.75 to 1.81
LABA/ICS vs LAMA	1.87	1.21 to 2.91	2.02	1.16 to 3.72
LABA/ICS vs LABA	1.82	1.41 to 2.36	1.93	1.29 to 3.22
LAMA vs LABA	0.97	0.66 to 1.44	0.96	0.62 to 1.49

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 70. Mean and median ranks: pneumonia in the low-risk population

Treatment group	Rank (from random-effects model)		
	Mean	Median	95% CrI
LAMA	1.6	1	1 to 3
LABA	1.8	2	1 to 3
LABA/LAMA	2.7	3	1 to 4
LABA/ICS	4.0	4	3 to 4

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Table 71. Within-class/group standard deviation for forced expiratory volume in 1 second at 12 months in the low-risk population: fixed-treatment-effect model with random-class

Treatment group	Median	95% CrI
LABA	0.273	0.022 to 1.190
LAMA	0.109	0.005 to 0.589
LABA/ICS	0.181	0.036 to 0.612

Table 71. Within-class/group standard deviation for forced expiratory volume in 1 second at 12 months in the low-risk population: fixed-treatment-effect model with random-class *(Continued)*

LABA/LAMA	0.181	0.036 to 0.612

CrI: credible interval; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Trials Register

Electronic searches: core databases

Database	Dates searched	Frequency of search
CENTRAL (via the Cochrane Register of Studies (CRS))	From inception	Monthly
MEDLINE (Ovid)	1946 onwards	Weekly
Embase (Ovid)	1974 onwards	Weekly
PsycINFO (Ovid)	1967 onwards	Monthly
CINAHL (EBSCO)	1937 onwards	Monthly
AMED (EBSCO)	From inception	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards

(*Continued*)

British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

Chronic obstructive pulmonary disease (COPD) search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema$.mp.
4. (chronic$ adj3 bronchiti$).mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify randomised controlled trials (RCTs)

1. exp "clinical trial [publication type)"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Appendix 2. Search strategy to identify relevant trials from the Cochrane Airways Trials Register

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 mometasone* AND formoterol*
#8 fluticasone* AND salmeterol*
#9 budesonide* AND formoterol*
#10 beclomethasone* AND formoterol*
#11 fluticasone* AND formoterol*
#12 Flutiform or Fostair or Simplyone
#13 fluticasone* AND vilanterol*
#14 mometasone* AND indacaterol*
#15 formoterol* and ciclesonide*
#16 QMF149
#17 GW685698 AND GW642444
#18 steroid* OR corticosteroid* or ICS
#19 (long-acting* or long NEXT acting*) NEAR beta*
#20 #18 AND #19
#21 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #20
#21 formoterol* AND aclidinium*
#22 indacaterol* AND glycopyrronium*
#23 indacaterol* AND tiotropium*
#24 olodaterol* AND tiotropium*
#25 vilanterol* AND umeclidinium*
#26 QVA149
#27 Ultibro or Stiolto or Duaklir Genuair
#28 Muscarinic* Next Antagonist*
#29 #19 AND #28
#30 #21 or # 22 or #23 or #24 or #25 or #26 or #27 or # 29
#31 combin* NEAR inhaler*
#32 FDC:ti,ab
#33 #21 or #30 or #31 or #32
#34 #6 AND #33
(In search line #4, MISC1 denotes the field in which the reference has been coded for condition, in this case, COPD)

Appendix 3. Tables of interventions and treatment groups in the NMAs

1. Population: high-risk

1.1.1 Moderate to severe exacerbations

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Indacaterol 150 μg once daily	LABA
3	Formoterol 9-12 μg twice daily	LABA
4	Tiotropium 18 μg once daily	LAMA
5	Glycopyrronium 50 μg once daily	LAMA
6	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
7	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
8	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
9	Salmeterol 50 twice daily + fluticasone 500 μg twice daily	LABA/ICS
10	Formoterol/budesonide 9/160 μg twice daily	LABA/ICS
11	Formoterol/budesonide 9/320 μg twice daily	LABA/ICS
12	Formoterol/beclomethasone 12/200 μg twice daily	LABA/ICS
13	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
14	Salmeterol 50 twice daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.1.2 Severe exacerbations

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Indacaterol 150 μg once daily	LABA
3	Tiotropium 18 μg once daily	LAMA
4	Glycopyrronium 50 μg once daily	LAMA

(*Continued*)

5	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
6	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
7	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
8	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
9	Salmeterol 50 twice daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.2.2 St George's Respiratory Questionnaire responders at 12 months

	Intervention	Treatment group
1	Salmeterol 50 twice daily	LABA
2	Indacaterol 150 once daily	LABA
3	Formoterol 9-12 twice daily	LABA
4	Tiotropium 18 once daily	LAMA
5	Glycopyrronium 50 once daily	LAMA
6	Salmeterol/fluticasone 50/250 twice daily	LABA/ICS
7	Salmeterol/fluticasone 50/500 twice daily	LABA/ICS
8	Formoterol/budesonide 12/400 twice daily DPI	LABA/ICS
9	Formoterol/beclomethasone 12/200 twice daily	LABA/ICS
10	Indacaterol/glycopyrronium 110/50 once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.3.1 Change from baseline in St George's Respiratory Questionnaire score at 3 months

	Intervention	Treatment group
1	Indacaterol 150 μg once daily	LABA
2	Salmeterol 50 μg twice daily	LABA
3	Formoterol 9-12 μg twice daily	LABA
4	Tiotropium 18 μg once daily	LAMA
5	Glycopyrronium 50 μg once daily	LAMA
6	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
7	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
8	Salmeterol 50 μg twice daily + fluticasone 250 μg twice daily	LABA/ICS
9	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
10	Indacaterol 150 μg once daily + budesonide 400 μg twice daily	LABA/ICS
11	Formoterol/budesonide 9/320 μg twice daily	LABA/ICS
12	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.3.2 Change from baseline in St George's Respiratory Questionnaire score at 6 months

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Indacaterol 150 μg once daily	LABA
3	Formoterol 9-12 μg twice daily	LABA
4	Tiotropium 18 μg once daily	LAMA
5	Glycopyrronium 50 μg once daily	LAMA
6	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS

(*Continued*)

7	Salmeterol/fluticasone 50/50 μg twice daily	LABA/ICS
8	Salmeterol 50 μg twice daily + fluticasone 250 μg twice daily	LABA/ICS
9	Indacaterol 150 μg once daily + budesonide 400 μg twice daily	LABA/ICS
10	budesonide/formoterol 160/9 μg twice daily	LABA/ICS
11	budesonide/formoterol 320/9 μg twice daily	LABA/ICS
12	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.3.3 Change from baseline in St George's Respiratory Questionnaire score at 12 months

	Intervention	**Treatment group**
1	Salmeterol 50 μg twice daily	LABA
2	Indacaterol 150 μg once daily	LABA
3	Formoterol 9 μg twice daily	LABA
4	Formoterol 12 μg twice daily	LABA
5	Tiotropium 18 μg once daily	LAMA
6	Glycopyrronium 50 μg once daily	LAMA
7	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
8	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
9	Salmeterol 50 μg twice daily + fluticasone 500 μg twice daily	LABA/ICS
10	Budesonide/formoterol 160/9 μg twice daily	LABA/ICS
11	Budesonide/formoterol 400/12 μg twice daily	LABA/ICS
12	Beclomethasone/formoterol 200/12 μg twice daily	LABA/ICS
13	Budesonide/formoterol 320/9 μg twice daily	LABA/ICS

(*Continued*)

14	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
15	Salmeterol 50 μg twice daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.5.1 Change from baseline in forced expiratory volume in 1 second at 3 months

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 9 μg twice daily	LABA
3	Formoterol 12 μg twice daily	LABA
4	Tiotropium 18 μg once daily	LAMA
5	Glycopyrronium 50 μg once daily	LAMA
6	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
7	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
8	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
9	Budesonide + indacaterol 400/150 μg twice daily	LABA/ICS
10	Budesonide/formoterol 320/9 μg twice daily	LABA/ICS
11	Beclomethasone/formoterol 200/12 μg twice daily	LABA/ICS
12	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.5.2 Change from baseline in forced expiratory volume in 1 second at 6 months

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 9 μg twice daily	LABA
3	Tiotropium 18 μg once daily	LAMA
4	Glycopyrronium 50 μg once daily	LAMA
5	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
6	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
7	Salmeterol 50 twice daily + fluticasone 250 μg twice daily	LABA/ICS
8	Budesonide + indacaterol 400/150 μg twice daily	LABA/ICS
9	Budesonide/formoterol 160/9 μg twice daily	LABA/ICS
10	Budesonide/formoterol 320/9 μg twice daily	LABA/ICS
11	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.5.3 Change from baseline in forced expiratory volume in 1 second at 12 months

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 9 μg twice daily	LABA
3	Formoterol 12 μg twice daily	LABA
4	Tiotropium 18 μg once daily	LAMA
5	Glycopyrronium 50 μg once daily	LAMA
6	Budesonide/formoterol 320/9 μg twice daily	LABA/ICS
7	Budesonide/formoterol 160/9 μg twice daily	LABA/ICS

(*Continued*)

8	Budesonide/formoterol 400/12 μg twice daily	LABA/ICS
9	Beclomethasone/formoterol 200/12 μg twice daily	LABA/ICS
10	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
11	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
12	Salmeterol 50 twice daily + fluticasone 500 μg twice daily	LABA/ICS
13	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.6 Mortality

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Indacaterol 150 μg once daily	LABA
3	Formoterol 9 μg twice daily	LABA
4	Formoterol 12 μg twice daily	LABA
5	Tiotropium 18 μg once daily	LAMA
6	Glycopyrronium 50 μg once daily	LAMA
7	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
8	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
9	Salmeterol 50 μg twice daily + fluticasone 500 μg twice daily	LABA/ICS
10	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
11	Salmeterol 50 twice daily + fluticasone 250 μg twice daily	LABA/ICS
12	Budesonide 400 μg twice daily + indacaterol 150 μg once daily	LABA/ICS
13	Budesonide/formoterol 320/9 μg twice daily	LABA/ICS

(*Continued*)

14	Budesonide/formoterol 160/9 μg twice daily	LABA/ICS
15	Budesonide/formoterol 400/12 μg	LABA/ICS
16	Beclomethasone/formoterol 200/12 μg	LABA/ICS
17	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
18	Salmeterol 50 twice daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.7.1 Total serious adverse events

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Indacaterol 150 μg once daily	LABA
3	Formoterol 9 μg twice daily	LABA
4	Formoterol 12 μg twice daily	LABA
5	Tiotropium 18 μg once daily	LAMA
6	Glycopyrronium 50 μg once daily	LAMA
7	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
8	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
9	Salmeterol 50 μg twice daily + fluticasone 500 μg twice daily	LABA/ICS
10	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
11	Budesonide 400 μg twice daily + indacaterol 150 μg once daily	LABA/ICS
12	Budesonide/formoterol 320/9 μg twice daily	LABA/ICS
13	Budesonide/formoterol 160/9 μg twice daily	LABA/ICS
14	Budesonide/formoterol 400/12 μg	LABA/ICS

(*Continued*)

15	Beclomethasone/formoterol 200/12 µg	LABA/ICS
16	Salmeterol 50 µg twice daily + fluticasone 250 µg twice daily	LABA/ICS
17	Indacaterol/glycopyrronium 110/50 µg once daily	LABA/LAMA
18	Salmeterol 50 µg twice daily + tiotropium 18 µg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.7.2 Chronic obstructive pulmonary disease serious adverse events

	Intervention	Treatment group
1	Salmeterol 50 µg twice daily	LABA
2	Indacaterol 150 µg once daily	LABA
3	Formoterol 9 µg twice daily	LABA
4	Tiotropium 18 µg once daily	LAMA
5	Glycopyrronium 50 µg once daily	LAMA
6	Salmeterol/fluticasone 50/250 µg twice daily	LABA/ICS
7	Salmeterol/fluticasone 50/500 µg twice daily	LABA/ICS
8	Salmeterol 50 µg twice daily + fluticasone 250 µg twice daily	LABA/ICS
9	Salmeterol 50 µg twice daily + fluticasone 500 µg twice daily	LABA/ICS
10	Vilanterol/fluticasone 25/100 µg once daily	LABA/ICS
11	Indacaterol 150 µg once daily + budesonide 400 µg twice daily	LABA/ICS
12	Budesonide/formoterol 160/9 µg twice daily	LABA/ICS
13	Budesonide/formoterol 320/9 µg twice daily	LABA/ICS
14	Indacaterol/glycopyrronium 110/50 µg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.7.3 Cardiac serious adverse events

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Indacaterol 150 μg once daily	LABA
3	Formoterol 9 μg twice daily	LABA
4	Formoterol 12 μg twice daily	LABA
5	Tiotropium 18 μg once daily	LAMA
6	Glycopyrronium 50 μg once daily	LAMA
7	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
8	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
9	Salmeterol 50 μg twice daily + fluticasone 500 μg twice daily	LABA/ICS
10	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
11	Fluticasone 250 μg + salmeterol 50 μg twice daily	LABA/ICS
12	Budesonide 400 μg twice daily + indacaterol 150 μg once daily	LABA/ICS
13	Budesonide/formoterol 160/9 μg twice daily	LABA/ICS
14	Budesonide/formoterol 320/9 μg twice daily	LABA/ICS
15	Beclomethasone/formoterol 200/12 μg	LABA/ICS
16	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.8 Dropouts due to adverse events

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Indacaterol 150 μg once daily	LABA

(*Continued*)

3	Formoterol 9 μg twice daily	LABA
4	Formoterol 12 μg twice daily	LABA
5	Tiotropium 18 μg once daily	LAMA
6	Glycopyrronium 50 μg once daily	LAMA
7	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
8	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
9	Salmeterol 50 μg twice daily + fluticasone 500 μg twice daily	LABA/ICS
10	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
11	Fluticasone 250 μg + salmeterol 50 μg twice daily	LABA/ICS
12	Budesonide 400 μg twice daily + indacaterol 150 μg once daily	LABA/ICS
13	Budesonide/formoterol 320/9 μg twice daily	LABA/ICS
14	Budesonide/formoterol 160/9 μg twice daily	LABA/ICS
15	Budesonide/formoterol 400/12 μg	LABA/ICS
16	Beclomethasone/formoterol 200/12	LABA/ICS
17	Indacaterol/glycopyrronium 110/50 once daily	LABA/LAMA
18	Salmeterol 50 twice daily + tiotropium 18 once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

1.9 Pneumonia

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Indacaterol 150 μg once daily	LABA
3	Formoterol 9 μg twice daily	LABA

(*Continued*)

4	Formoterol 12 μg twice daily	LABA
5	Tiotropium 18 μg once daily	LAMA
6	Glycopyrronium 50 μg once daily	LAMA
7	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
8	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
9	Salmeterol 50 twice daily + fluticasone 500 μg twice daily	LABA/ICS
10	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
11	Budesonide/formoterol 160/9 μg twice daily	LABA/ICS
12	Budesonide/formoterol 320/9 μg twice daily	LABA/ICS
13	Budesonide/formoterol 400/12 μg	LABA/ICS
14	Beclomethasone/formoterol 200/12 μg	LABA/ICS
15	Budesonide 400 μg twice daily + indacaterol 150 μg once daily	LABA/ICS
16	Fluticasone 250 μg + salmeterol 50 μg twice daily	LABA/ICS
17	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
18	Salmeterol 50 μg twice daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2 Population: low-risk

2.1.1 Moderate to severe exacerbations

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 9-12 μg twice daily	LABA
3	Indacaterol 75 μg once daily	LABA

(*Continued*)

4	Indacaterol 150 μg once daily	LABA
5	Indacaterol 300 μg once daily	LABA
6	Tiotropium 18 μg once daily	LAMA
7	Tiotropium 5 μg once daily	LAMA
8	Aclidinium 400 μg twice daily	LAMA
9	Umeclidinium 62.5 μg once daily	LAMA
10	Glycopyrronium 50 μg once daily	LAMA
11	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
12	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
13	Salmeterol/fluticasone 42/230 μg (HFA) twice daily	LABA/ICS
14	Formoterol/mometasone 200/10 μg twice daily	LABA/ICS
15	Formoterol/mometasone 400/10 μg twice daily	LABA/ICS
16	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
17	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
18	Indacaterol/glycopyrronium 27.5/12.5 μg twice daily	LABA/LAMA
19	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
20	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA
21	Indacaterol 150 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
22	Tiotropium 18 μg once daily + formoterol 10 μg twice daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.1.2 Severe exacerbations

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 9-12 μg twice daily	LABA
3	Indacaterol 150 μg once daily	LABA
4	Tiotropium 18 μg once daily	LAMA
5	Tiotropium 5 μg once daily	LAMA
6	Umeclidinium 62.5 μg once daily	LAMA
7	Glycopyrronium 50 μg once daily	LAMA
8	Salmetrol/fluticasone 50/250 μg twice daily	LABA/ICS
9	Salmetrol/fluticasone 50/500 μg twice daily	LABA/ICS
10	Salmetrol/fluticasone 42/230 μg (HFA) twice daily	LABA/ICS
11	Formoterol/mometasone 200/10 μg twice daily	LABA/ICS
12	Formoterol/mometasone 400/10 μg twice daily	LABA/ICS
13	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
14	Vilaterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
15	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
16	Formterol/aclidinium 12/400 μg twice daily	LABA/LAMA
17	Indacaterol 150 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
18	Formoterol 10-12 μg twice daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.2.1 St George's Respiratory Questionnaire responders at 3 months

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Indacaterol 150 μg once daily	LABA
3	Formoterol 4.5 μg twice daily	LABA
4	Formoterol 9-12 μg twice daily	LABA
5	Tiotropium 18 μg once daily	LAMA
6	Umeclidinium 62.5 μg once daily	LAMA
7	Glycopyrronium 50 μg once daily	LAMA
8	Glycopyrronium 15.6 μg twice daily	LAMA
9	Tiotropium 5 μg once daily	LAMA
10	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
11	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
12	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
13	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
14	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
15	Indacaterol 150 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
16	Indacaterol/glycopyrronium 27.5/12.5 μg	LABA/LAMA
17	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.2.2 St George's Respiratory Questionnaire responders at 6 months

	Intervention	**Treatment group**
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 9-12 μg twice daily	LABA
3	Indacaterol 150 μg once daily	LABA
4	Indacaterol 300 μg once daily	LABA
5	Tiotropium 18 μg once daily	LAMA
6	Aclidinium 400 μg twice daily	LAMA
7	Umeclidinium 62.5 μg once daily	LAMA
8	Glycopyrronium 15.6 μg twice daily	LAMA
9	Glycopyrronium 50 μg once daily	LAMA
10	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
11	Formoterol/mometasone 200/10 μg twice daily	LABA/ICS
12	Formoterol/mometasone 400/10 μg twice daily	LABA/ICS
13	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
14	Formoterol/glycopyrronium 9.6/18 μg twice daily	LABA/LAMA
15	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
16	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA
17	Formoterol 10-12 μg twice daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.3.1 Change from baseline in St George's Respiratory Questionnaire score at 3 months

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Indacaterol 150 μg once daily	LABA
3	Indacaterol 300 μg once daily	LABA
4	Formoterol 4.5 μg twice daily	LABA
5	Formoterol 9-12 μg twice daily	LABA
6	Tiotropium 18 μg once daily	LAMA
7	Umeclidinium 62.5 μg once daily	LAMA
8	Glycopyrronium 50 μg once daily	LAMA
9	Glycopyrronium 15.6 μg twice daily	LAMA
10	Tiotropium 5 μg once daily	LAMA
11	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
12	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
13	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
14	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
15	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
16	Indacaterol/ glycopyrronium 27.5/12.5 μg twice daily	LABA/LAMA
17	Indacaterol 150 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
18	Olodaterol 5 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
19	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.3.2 Change from baseline in St George's Respiratory Questionnaire score at 6 months

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 9-12 μg twice daily	LABA
3	Indacaterol 150 μg once daily	LABA
4	Indacaterol 300 μg once daily	LABA
5	Tiotropium 18 μg once daily	LAMA
6	Aclidinium 400 μg twice daily	LAMA
7	Umeclidinium 62.5 μg once daily	LAMA
8	Glycopyrronium 15.6 μg twice daily	LAMA
9	Glycopyrronium 50 μg once daily	LAMA
10	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
11	Formoterol/mometasone 200/10 μg twice daily	LABA/ICS
12	Formoterol/mometasone 400/10 μg twice daily	LABA/ICS
13	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
14	Formoterol/glycopyrronium 9.6/18 μg twice daily	LABA/LAMA
15	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
16	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA
17	Formoterol 10-12 μg twice daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.3.3 Change from baseline in St George's Respiratory Questionnaire score at 12 months

	Intervention	Treatment group
1	Formoterol 9-12 μg twice daily	LABA
2	Salmeterol 50 μg twice daily	LABA
3	Tiotropium 18 μg once daily	LAMA
4	Aclidinium 400 μg twice daily	LAMA
5	Glycopyrronium 15.6 μg twice daily	LAMA
6	Glycopyrronium 50 μg once daily	LAMA
7	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
8	Formoterol/glycopyrronium 9.6/18 μg twice daily	LABA/LAMA
9	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
10	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.4.1 Transition Dyspnea Index at 3 months

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Indacaterol 150 μg once daily	LABA
3	Indacaterol 300 μg once daily	LABA
4	Olodaterol 5 μg once daily	LABA
5	Formoterol 9-12 μg twice daily	LABA
6	Tiotropium 18 μg once daily	LAMA
7	Umeclidinium 62.5 μg once daily	LAMA
8	Glycopyrronium 50 μg once daily	LAMA

(*Continued*)

9	Tiotropium 5 μg once daily	LAMA
10	Glycopyrronium 15.6 μg twice daily	LAMA
11	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
12	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
13	ICS/LABA free or fixed combination	LABA/ICS
14	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
15	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
16	Indacaterol 150 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
17	Indacaterol 110 μg once daily + glycopyrronium 50 μg once daily	LABA/LAMA
18	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA
19	Indacaterol/glycopyrronium 27.5/12.5 μg twice daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.4.2 Transition Dyspnea Index at 6 months

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 9-12 μg twice daily	LABA
3	Indacaterol 150 μg once daily	LABA
4	Olodaterol 5 μg once daily	LABA
5	Tiotropium 18 μg once daily	LAMA
6	Tiotropium 5 μg once daily	LAMA
7	Aclidinium 400 μg twice daily	LAMA
8	Umeclidinium 62.5 μg once daily	LAMA

(*Continued*)

9	Glycopyrronium 50 μg once daily	LAMA
10	Salmeterol/fluticasone 250/50 μg twice daily	LABA/ICS
11	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
12	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
13	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
14	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA
15	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA
16	Formoterol 10-12 μg twice daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.4.3 Transition Dyspnea Index at 12 months

	Intervention	Treatment group
1	Formoterol 9-12 μg twice daily	LABA
2	Indacaterol 300 μg once daily	LABA
3	Olodaterol 5 μg once daily	LABA
4	Tiotropium 18 μg once daily	LAMA
5	Tiotropium 5 μg once daily	LAMA
6	Aclidinium 400 μg twice daily	LAMA
7	Glycopyrronium 15.6 μg twice daily	LAMA
8	Formoterol/glycopyrronium 9.6/18 μg twice daily	LABA/LAMA
9	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA
10	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.5.1 Change from baseline in forced expiratory volume in 1 second at 3 months

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 9-12 μg twice daily	LABA
3	Indacaterol 75 μg once daily	LABA
4	Indacaterol 150 μg once daily	LABA
5	Indacaterol 300 μg once daily	LABA
6	Olodaterol 5 μg once daily	LABA
7	Tiotropium 18 once daily	LAMA
8	Tiotropium 5 once daily	LAMA
9	Umeclidinium 62.5 μg once daily	LAMA
10	Glycopyrronium 15.6 μg twice daily	LAMA
11	Glycopyrronium 50 μg once daily	LAMA
12	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
13	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
14	Salmeterol/fluticasone 42/230 μg (HFA) twice daily	LABA/ICS
15	Formoterol/mometasone 200/10 μg twice daily	LABA/ICS
16	Formoterol/mometasone 400/10 μg twice daily	LABA/ICS
17	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
18	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
19	Indacaterol/glycopyrronium 27.5/15.6 μg twice daily	LABA/LAMA
20	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
21	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA
22	Indacaterol 150 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
23	Olodaterol 5 μg once daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.5.2 Change from baseline in forced expiratory volume in 1 second at 6 months

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 9-12 μg twice daily	LABA
3	Indacaterol 75 μg once daily	LABA
4	Indacaterol 150 μg once daily	LABA
5	Indacaterol 300 μg once daily	LABA
6	Olodaterol 5 μg once daily	LABA
7	Tiotropium 18 μg once daily	LAMA
8	Tiotropium 5 μg once daily	LAMA
9	Aclidinium 400 μg twice daily	LAMA
10	Umeclidinium 62.5 μg once daily	LAMA
11	Glycopyrronium 15.6 μg twice daily	LAMA
12	Glycopyrronium 50 μg once daily	LAMA
13	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
14	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
15	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
16	Formoterol/glycopyrronium 9.6/18 μg twice daily	LABA/LAMA
17	Indacaterol/glycopyrronium 27.5/15.6 μg twice daily	LABA/LAMA
18	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
19	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA
20	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA

(*Continued)*

21	Formoterol 10-12 μg twice daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.5.3 Change from baseline in forced expiratory volume in 1 second at 12 months

	Intervention	Treatment group
1	Formoterol 9-12 μg twice daily	LABA
2	Indacaterol 75 μg once daily	LABA
3	Olodaterol 5 μg once daily	LABA
4	Tiotropium 18 μg once daily	LAMA
5	Tiotropium 5 μg once daily	LAMA
6	Aclidinium 400 μg twice daily	LAMA
7	Glycopyrronium 15.6 μg twice daily	LAMA
8	Glycopyrronium 50 μg once daily	LAMA
9	Formoterol/glycopyrronium 9.6/18 μg twice daily	LABA/LAMA
10	Indacaterol/glycopyrronium 27.5/15.6 μg twice daily	LABA/LAMA
11	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
12	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA
13	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.6 Mortality

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 4.5 μg twice daily	LABA
3	Formoterol 9-12 μg twice daily	LABA
4	Indacaterol 75 μg once daily	LABA
5	Indacaterol 150 μg once daily	LABA
6	Indacaterol 300 μg once daily	LABA
7	Olodaterol 5 μg once daily	LABA
8	Tiotropium 18 μg once daily	LAMA
9	Tiotropium 5 μg once daily	LAMA
10	Aclidinium 400 μg twice daily	LAMA
11	Umeclidinium 62.5 μg once daily	LAMA
12	Glycopyrronium 15.6 μg twice daily	LAMA
13	Glycopyrronium 50 μg once daily	LAMA
14	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
15	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
16	Formoterol/mometasone 200/10 μg twice daily	LABA/ICS
17	Formoterol/mometasone 400/10 μg twice daily	LABA/ICS
18	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
19	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
20	Formoterol/glycopyrronium 9.6/18 μg twice daily	LABA/LAMA
21	Indacaterol/glycopyrronium 27.5/15.6 μg twice daily	LABA/LAMA
22	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
23	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA

(*Continued*)

24	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA
25	Indacaterol 150 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
26	Formoterol 10-12 μg twice daily + tiotropium 18 μg once daily	LABA/LAMA
27	Olodaterol 5 μg once daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.7.1 Total serious adverse events

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 4.5 μg twice daily	LABA
3	Formoterol 9-12 μg twice daily	LABA
4	Indacaterol 75 μg once daily	LABA
5	Indacaterol 150 μg once daily	LABA
6	Indacaterol 300 μg once daily	LABA
7	Olodaterol 5 μg once daily	LABA
8	Tiotropium 18 μg once daily	LAMA
9	Tiotropium 5 μg once daily	LAMA
10	Aclidinium 400 μg twice daily	LAMA
11	Umeclidinium 62.5 μg once daily	LAMA
12	Glycopyrronium 15.6 μg twice daily	LAMA
13	Glycopyrronium 50 μg once daily	LAMA
14	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
15	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS

(*Continued*)

16	Salmeterol/fluticasone 42/230 μg (HFA) twice daily	LABA/ICS
17	Formoterol/mometasone 200/10 μg twice daily	LABA/ICS
18	Formoterol/mometasone 400/10 μg twice daily	LABA/ICS
19	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
20	ICS/LABA free or fixed combination	LABA/ICS
21	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
22	Formoterol/glycopyrronium 9.6/18 μg twice daily	LABA/LAMA
23	Indacaterol/glycopyrronium 27.5/15.6 μg twice daily	LABA/LAMA
24	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
25	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA
26	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA
27	Indacaterol 150 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
28	Formoterol 10-12 μg twice daily + tiotropium 18 μg once daily	LABA/LAMA
29	Olodaterol 5 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
30	Indacaterol 110 μg once daily + glycopyrronium 50 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.7.2 Chronic obstructive pulmonary disease serious adverse events

1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 4.5 μg twice daily	LABA
3	Formoterol 9-12 μg twice daily	LABA
4	Indacaterol 75 μg once daily	LABA
5	Indacaterol 150 μg once daily	LABA

(*Continued*)

6	Indacaterol 300 μg once daily	LABA
7	Olodaterol 5 μg once daily	LABA
8	Tiotropium 18 μg once daily	LAMA
9	Tiotropium 5 μg once daily	LAMA
10	Aclidinium 400 μg twice daily	LAMA
11	Umeclidinium 62.5 μg once daily	LAMA
12	Glycopyrronium 15.6 μg twice daily	LAMA
13	Glycopyrronium 50 μg once daily	LAMA
14	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
15	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
16	Salmeterol/fluticasone 42/230 μg (HFA) twice daily	LABA/ICS
17	Formoterol/mometasone 200/10 μg twice daily	LABA/ICS
18	Formoterol/mometasone 400/10 μg twice daily	LABA/ICS
19	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
20	ICS/LABA free or fixed combination	LABA/ICS
21	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
22	Formoterol/glycopyrronium 9.6/18 μg twice daily	LABA/LAMA
23	Indacaterol/glycopyrronium 27.5/15.6 μg twice daily	LABA/LAMA
24	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
25	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA
26	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA
27	Indacaterol 150 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
28	Formoterol 10-12 μg twice daily + tiotropium 18 μg once daily	LABA/LAMA

(*Continued*)

29	Olodaterol 5 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
30	Indacaterol 110 μg once daily + glycopyrronium 50 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.7.3 Cardiac serious adverse events

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 4.5 μg twice daily	LABA
3	Formoterol 9-12 μg twice daily	LABA
4	Indacaterol 75 μg once daily	LABA
5	Indacaterol 150 μg once daily	LABA
6	Indacaterol 300 μg once daily	LABA
7	Olodaterol 5 μg once daily	LABA
8	Tiotropium 18 μg once daily	LAMA
9	Tiotropium 5 μg once daily	LAMA
10	Aclidinium 400 μg twice daily	LAMA
11	Umeclidinium 62.5 μg once daily	LAMA
12	Glycopyrronium 15.6 μg twice daily	LAMA
13	Glycopyrronium 50 μg once daily	LAMA
14	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
15	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
16	Formoterol/mometasone 200/10 μg twice daily	LABA/ICS
17	Formoterol/mometasone 400/10 μg twice daily	LABA/ICS

(*Continued*)

18	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
19	ICS/LABA free or fixed combination	LABA/ICS
20	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
21	Formoterol/glycopyrronium 9.6/18 μg twice daily	LABA/LAMA
22	Indacaterol/glycopyrronium 27.5/15.6 μg twice daily	LABA/LAMA
23	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
24	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA
25	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA
26	Indacaterol 150 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
27	Formoterol 10-12 μg twice daily + tiotropium 18 μg once daily	LABA/LAMA
28	Olodaterol 5 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
29	Indacaterol 110 μg once daily + glycopyrronium 50 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.8 Dropouts

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 4.5 μg twice daily	LABA
3	Formoterol 9-12 μg twice daily	LABA
4	Indacaterol 75 μg once daily	LABA
5	Indacaterol 150 μg once daily	LABA
6	Indacaterol 300 μg once daily	LABA
7	Olodaterol 5 μg once daily	LABA

(*Continued*)

8	Tiotropium 18 μg once daily	LAMA
9	Tiotropium 5 μg once daily	LAMA
10	Aclidinium 400 μg twice daily	LAMA
11	Umeclidinium 62.5 μg once daily	LAMA
12	Glycopyrronium 15.6 μg twice daily	LAMA
13	Glycopyrronium 50 μg once daily	LAMA
14	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
15	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
16	Salmeterol/fluticasone 42/230 μg twice daily	LABA/ICS
17	Formoterol/mometasone 200/10 μg twice daily	LABA/ICS
18	Formoterol/mometasone 400/10 μg twice daily	LABA/ICS
19	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
20	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
21	Formoterol/glycopyrronium 9.6/18 μg twice daily	LABA/LAMA
22	Indacaterol/glycopyrronium 27.5/15.6 μg twice daily	LABA/LAMA
23	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
24	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA
25	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA
26	Indacaterol 150 once daily + tiotropium 18 μg once daily	LABA/LAMA
27	Formoterol 10-12 twice daily + tiotropium 18 μg once daily	LABA/LAMA
28	Olodaterol 5 once daily + tiotropium 18 μg once daily	LABA/LAMA
29	Indacaterol 110 μg once daily + glycopyrronium 50 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

2.9 Pneumonia

	Intervention	Treatment group
1	Salmeterol 50 μg twice daily	LABA
2	Formoterol 4.5 μg twice daily	LABA
3	Formoterol 9-12 μg twice daily	LABA
4	Indacaterol 75 μg once daily	LABA
5	Indacaterol 150 μg once daily	LABA
6	Indacaterol 300 μg once daily	LABA
7	Olodaterol 5 μg once daily	LABA
8	Tiotropium 18 μg once daily	LAMA
9	Tiotropium 5 μg once daily	LAMA
10	Aclidinium 400 μg twice daily	LAMA
11	Umeclidinium 62.5 μg once daily	LAMA
12	Glycopyrronium 15.6 μg twice daily	LAMA
13	Glycopyrronium 50 μg once daily	LAMA
14	Salmeterol/fluticasone 50/250 μg twice daily	LABA/ICS
15	Salmeterol/fluticasone 50/500 μg twice daily	LABA/ICS
16	Salmeterol/fluticasone 42/230 μg twice daily	LABA/ICS
17	Formoterol/mometasone 200/10 μg twice daily	LABA/ICS
18	Formoterol/mometasone 400/10 μg twice daily	LABA/ICS
19	Vilanterol/fluticasone 25/100 μg once daily	LABA/ICS
20	ICS/LABA free or fixed combination	LABA/ICS
21	Vilanterol/umeclidinium 25/62.5 μg once daily	LABA/LAMA
22	Formoterol/glycopyrronium 9.6/18 μg twice daily	LABA/LAMA

(*Continued*)

23	Indacaterol/glycopyrronium 27.5/15.6 μg twice daily	LABA/LAMA
24	Indacaterol/glycopyrronium 110/50 μg once daily	LABA/LAMA
25	Olodaterol/tiotropium 5/5 μg once daily	LABA/LAMA
26	Formoterol/aclidinium 12/400 μg twice daily	LABA/LAMA
27	Indacaterol 150 μg once daily + tiotropium 18 μg once daily	LABA/LAMA
28	Formoterol 10-12 μg twice daily + tiotropium 18 μg once daily	LABA/LAMA
29	Olodaterol 5 μg once daily + tiotropium 18 μg once daily	LABA/LAMA

ICS: inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist

Appendix 4. Model fit description and statistics

Population: high-risk

Outcome: moderate to severe exacerbations

We fitted random- and fixed-treatment-effects network meta-analysis (NMA) models with fixed-class effects. The random-effects model had a better fit than the fixed-effect model with lower deviance information criterion (DIC) and between-study heterogeneity was low (standard deviation (SD) 0.07, 95% credible interval (CrI) 0.008 to 0.14). We considered a random-class model with fixed-treatment effects, which only slightly improved fit compared to the fixed-treatment-effect model with fixed-class. We chose the random-treatment-effects model with fixed-class effects as it had the lowest DIC.

The inconsistency model with random treatment effects (and fixed-class effects), did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. Plotting each data point's contribution to the residual deviance in the NMA (consistency), and inconsistency models showed small improvements for two data points in the inconsistency model with other points fitting worse (Figure 3c). Reported results are therefore based on the random-treatment-effects NMA model with fixed-class effects assuming consistency.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	42.65	0.07 (0.008 to 0.14)	24.52
Fixed-effect model	48.22		36.45
Random-effects inconsistency model	42.04	0.05 (0.003 to 0.13)	24.31

(*Continued*)

Random-class-effects models			
Fixed-effect model	49.36		33.33

[a] compare to 27 data points

Outcome: severe exacerbations

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was low (SD 0.07, 95% CrI 0.003 to 0.26). We chose the fixed-effect model as it had the lowest DIC.

The inconsistency model with fixed-treatment effects (and fixed-class effects) did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA and inconsistency models, which showed no substantial improvement in fit for any data point (Figure 4). Reported results are therefore based on the fixed-effect NMA model, assuming consistency with results based on the random-effects model also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	71.89	0.07 (0.003 to 0.26)	16.64
Fixed-effect model	70.30		17.44
Fixed-effect inconsistency model	73.68		18.84

[a] compare to 19 data points

Outcome: St George's Respiratory Questionnaire responders at 12 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The random-effects model had a better fit than the fixed-effect model although their DIC were comparable and between-study heterogeneity was moderate (SD 0.26, 95% CrI 0.03 to 1.01). We considered a random-class model with fixed-treatment effects but this did not meaningfully improve fit. As there were not enough data to estimate the within-class variance for the LAMA and LABA/LAMA groups, we assumed that these were equal to the variance in the other monotherapy and combination class respectively. We chose the fixed-treatment-effect model with fixed-class effects as it is the simplest and had comparable DIC to the other models.

The inconsistency model with fixed-treatment effects (and fixed-class effects) did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. Plotting each data point's contribution to the residual deviance in the NMA (consistency) and inconsistency models showed some improvement in fit for data points from one study (Figure 6c). Reported results are based on the fixed-treatment-effect NMA model with fixed-class effects assuming consistency. Results based on the random-treatment-effects model with fixed-classes are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	137.86	0.16 (0.01 to 0.48)	16.91
Fixed-effect model	139.08		22.01
Fixed-effect inconsistency model	141.81		22.78
Random-class-effects models: class 2 uses variance from class 1, class 4 from class 3			
Fixed-effect model	144.12		22.17

[a] compare to 16 data points

Outcome: change from baseline in St George's Respiratory Questionnaire score at 3 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was moderate (SD 0.66, 95% CrI 0.03 to 2.93). We chose the fixed-treatment-effect model as it had the lowest DIC. The inconsistency model with fixed-treatment effects did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA (consistency), and inconsistency models, which showed an equal or better fit of points in the consistency model compared to the inconsistency model (Figure 7c). Reported results are therefore based on the fixed-treatment-effects NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	60.89	0.66 (0.03 to 2.93)	20.39
Fixed-effect model	59.35		21.26
Fixed-effect inconsistency model	62.90		22.84

[a] compare to 19 data points

Outcome: change from baseline in St George's Respiratory Questionnaire score at 6 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was moderate (SD 0.61, 95% CrI 0.31 to 2.03). We chose the fixed-treatment-effect model as it had the lowest DIC.

The inconsistency model with fixed-treatment effects did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA (consistency) and inconsistency models, which showed an equal or better fit of points in the consistency model compared to the inconsistency model (Figure 8c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	65.03	0.61 (0.31 to 2.03)	22.94
Fixed-effect model	64.00		25.08
Fixed-effect inconsistency model	66.70		25.79

[a] compare to 22 data points

Outcome: change from baseline in St George's Respiratory Questionnaire score at 12 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The random-effects model had a better fit than the fixed-effect model but comparable DIC and between-study heterogeneity was moderate (SD 0.81, 95% CrI 0.12 to 1.75). We considered a random-class model with fixed-treatment effects which only slightly improved fit compared to the fixed-treatment-effect model with fixed-class. As there were not enough data to estimate the within-class variance for the LAMA and LABA/LAMA groups, we assumed that these were equal to the variance in the other monotherapy and combination group respectively. We chose the fixed-treatment-effect model with fixed-class effects as it had the lowest DIC.

The inconsistency model with fixed-treatment effects (and fixed-class effects) did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. Plotting each data point's contribution to the residual deviance in the NMA (consistency) and inconsistency models showed a small improvement for data points from one study in the inconsistency model with other points fitting worse (Figure 9c).

Reported results are therefore based on the fixed-effect NMA model, assuming consistency with results based on the random-effects model also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	94.26	0.81 (0.12 to 1.75)	31.42
Fixed-effect model	96.60		39.8
Fixed-effect inconsistency model	96.96		38.2
Random-class-effects models			
Fixed-effect model	98.69		37.05

[a] compare to 32 data points

Outcome: change from baseline in forced expiratory volume in 1 second at 3 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well with equivalent DIC and low between-study heterogeneity (SD 0.01, 95% CrI 0.00 to 0.04). The fixed-effect model with fixed-class effects was chosen as it is the simplest.

The inconsistency model with fixed-treatment effects and fixed-class effects showed a very small improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA (consistency) and inconsistency models, which showed no substantial improvement in fit for any data point (Figure 11c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	−114.44	0.01 (0 to 0.04)	22.9
Fixed-effect model	−114.95		26.0
Fixed-effect inconsistency model	−115.14		24.8

[a] compare to 23 data points

Outcome: change from baseline in forced expiratory volume in 1 second at 6 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was low (SD = 0.02, 95% CrI 0 to 0.05). The fixed-effect model with fixed-class effects was chosen as it had the lowest DIC.

The inconsistency model with fixed-treatment effects and fixed-class effects did not show improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA (consistency) and inconsistency models, which showed no substantial improvement in fit for any data point (Figure 12c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	−103.62	0.02 (0.00 to 0.05)	22.70
Fixed-effect model	−103.97		25.87
Fixed-effect inconsistency model	−102.38		26.47

[a] compare to 24 data points

Outcome: change from baseline in forced expiratory volume in 1 second at 12 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was low (SD 0.01, 95% CrI 0.00 to 0.03). The fixed-effect model with fixed-class effects was chosen as it had the lowest DIC.

The inconsistency model with fixed-treatment effects and fixed-class effects did not show improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA (consistency) and inconsistency models, which showed no improvement in fit for any data point (Figure 13c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	−128.14	0.01 (0.00 to 0.03)	26.19
Fixed-effect model	−129.43		28.16
Fixed-effect inconsistency model	−128.31		28.28

[a] compare to 29 data points

Outcome: mortality

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was moderate (SD 0.17, 95% CrI 0.01 to 0.49). The fixed-effect model with fixed-class effects was chosen as it had the lowest DIC.

The inconsistency model with fixed-treatment effects and fixed-class effects showed a small improvement in fit compared to the NMA model assuming consistency. Plotting each data point's contribution to the residual deviance in the NMA (consistency) and inconsistency models, which showed some improvement in fit for data points from one study suggesting a possibility of inconsistency (Figure 15c).

Reported results are based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency although results should be interpreted with caution due to some evidence of inconsistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	271.00	0.17 (0.009 to 0.49)	51.45
Fixed-effect model	269.87		53.87
Fixed-effect inconsistency model	268.35		50.36

[a] compare to 53 data points

Outcome: total serious adverse events

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was very low (SD 0.05, 95% CrI 0.00 to 0.17). The fixed-effect model with fixed-class effects was chosen as it had the lowest DIC.

The inconsistency model with fixed-treatment effects and fixed-class effects showed no improvement in fit compared to the NMA model assuming consistency. Plotting each data point's contribution to the residual deviance in the NMA (consistency) and inconsistency models confirmed this as there was no improvement in fit for any data points in the inconsistency model (Figure 16c).

Reported results are based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	378.46	0.06 (0.002 to 0.17)	49.12
Fixed-effect model	376.7		50.94
Fixed-effect inconsistency model	379.24		51.44

[a] compare to 53 data points

Outcome: COPD serious adverse events

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was very low (SD 0.06, 95% CrI 0.00 to 0.21). The fixed-effect model with fixed-class effects was chosen as it had the lowest DIC.

The inconsistency model with fixed-treatment effects and fixed-class effects showed no improvement in fit compared to the NMA model assuming consistency. Plotting each data point's contribution to the residual deviance in the NMA (consistency) and inconsistency models confirmed this as there was no improvement in fit for any data points in the inconsistency model (Figure 17c).

Reported results are based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	283.74	0.06 (0.002 to 0.21)	42.55
Fixed-effect model	282.07		43.21
Fixed-effect inconsistency model	285.67		44.73

[a] compare to 44 data points

Outcome: cardiac serious adverse events

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The random-effects model had a better fit than the fixed-effect model with a slightly lower DIC although the posterior mean of the residual deviance was still considerably larger than the number of data points, and the between-study heterogeneity was moderate (SD 0.28 to 95% CrI 0.02 to 0.67). Random-class models with fixed- and random-treatment effects were fitted, which improved fit compared to the fixed-class models. As there were not enough data to estimate the within-class variance for the LABA/LAMA group, we assumed that this was equal to the variance in the other combination group (LABA/ICS). DIC was lowest for the random-treatment-effects model with a fixed-class so we chose this model. However, note that this DIC differed by only 1 point from the DIC for the fixed-treatment-effect model with a fixed-class.
The inconsistency models with random-treatment effects (and fixed-class), showed no improvement in fit and DIC compared to the NMA model assuming consistency to suggesting no evidence of inconsistency. Plotting each data point's contribution to the residual deviance in the NMA and inconsistency models confirmed this as there was no improvement in fit for any points in the inconsistency model (Figure 18c).
Reported results are therefore based on the random-treatment-effects NMA model with fixed-class effects to assuming consistency. Results based on the fixed-treatment-effect model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	256.42	0.28 (0.02, 0.67)	51.51
Fixed-effect model	257.45		59.83
Fixed-effect inconsistency model	260.69		61.06
Random-class-effects models			
Random-effects model	253.42	0.23 (0.01, 0.65)	44.88
Fixed-effect model	253.13		48.23

[a] compare to 42 data points

Outcome: dropouts due to adverse events

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was very low (SD 0.05 to 95% CrI 0.00 to 0.18). The fixed-effect model with fixed-class effects was chosen as it had the lowest DIC.
The inconsistency model with fixed-treatment effects and fixed-class effects showed no improvement in fit compared to the NMA model assuming consistency. Plotting each data point's contribution to the residual deviance in the NMA (consistency) and inconsistency models confirmed this as there was no improvement in fit for any data points in the inconsistency model (Figure 19c).
Reported results are based on the fixed-treatment-effect NMA model with fixed-class effects to assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	344.54	0.05 (0.002 to 0.18)	45.35
Fixed-effect model	342.43		45.35
Fixed-effect inconsistency model	345.77		46.7

[a]compare to 55 data points

Outcome: pneumonia

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The posterior mean of the residual deviance was substantially larger than the number of data points for both models and the between-study heterogeneity was moderate (SD 0.18, 95% CrI 0.01 to 0.61). Random-class models with fixed- and random-treatment-effects were fitted and although model fit was improved, the DIC was comparable to the fixed-class models. As there were not enough data to estimate the within-class variance for the LAMA and LABA/LAMA groups, we assumed that these were equal to the variance in the other monotherapy and combination groups respectively. The fixed-treatment-effect model with fixed-class had the lowest DIC so we chose this model.

The inconsistency model with fixed-treatment effects (and fixed-class), showed no improvement in fit or DIC compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA and inconsistency models, where fit was the same or better for the consistency model for most data points (Figure 20c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison. Results should be interpreted with some caution due to poor model fit, which can be attributed to studies with zero cells.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	280.12	0.18 (0.01 to 0.61)	60.01
Fixed-effect model	278.71		63.19
Fixed-effect inconsistency model	282.65		65.11
Random-class-effects models			
Fixed-effect model	281.64		60.95
Random-effects model	281.35	0.24 (0.01 to 0.71)	56.87

[a]compare to 53 data points

Population: low-risk

Outcome: moderate to severe chronic obstructive pulmonary disease exacerbations

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The random-effects model had a better fit than the fixed-effect model although their DIC were comparable and between-study heterogeneity was low (SD 0.054, 95% CrI 0.002 to 0.14). We considered a random-class model with fixed-treatment effects but this did not meaningfully improve fit. We chose the fixed-treatment-effect model with fixed-class effects as it is the simplest and had comparable DIC to the other models.

The inconsistency model with fixed-treatment effects (and fixed-class effects) did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA (consistency) and inconsistency models, which showed no substantial improvement in fit for any data point (Figure 21c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects assuming consistency. Results based on the random-treatment-effects model with fixed-classes are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	386.49	0.05 (0.002 to 0.14)	76.97
Fixed-effect model	387.13		81.9
Fixed-effect inconsistency model	390.02		81.8
Random-class-effects models			
Fixed-effect model	392.54		79.89

[a] compare to 72 data points

Outcome: severe chronic obstructive pulmonary disease exacerbations

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The random-effects model had a better fit than the fixed-effect model although the latter had lower DIC and between-study heterogeneity was low (SD 0.10, 95% CrI 0.006 to 0.43). A random-class model with fixed-treatment effect was considered but this did not improve fit so we chose the fixed-effect model with fixed-class effects as it had the lowest DIC.

The inconsistency model with fixed-treatment effects and fixed-class effects did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA (consistency), and inconsistency models, which showed no substantial improvement in fit for any data point (Figure 22c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	270.29	0.10 (0.006 to 0.43)	64.82
Fixed-effect model	268.61		66.19
Fixed-effect inconsistency model	273.57		68.36
Random-class-effects models			
Fixed-effect model	275.61		68.46

[a] compare to 60 data points

Outcome: St George's Respiratory Questionnaire responders at 3 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was low (SD 0.04, 95% CrI 0.002 to 0.15). We chose the fixed-treatment-effect model as it had the lowest DIC. The inconsistency model with fixed-treatment effects did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA (consistency) and inconsistency models, which showed an equal or better fit of points in the consistency model compared to the inconsistency model (Figure 24c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	337.64	0.04 (0.002 to 0.15)	39.84
Fixed-effect model	335.70		40.29
Fixed-effect inconsistency model	339.79		42.32

[a] compare to 44 data points

Outcome: St George's Respiratory Questionnaire responders at 6 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The random-effects model had a better fit than the fixed-effect model with a lower DIC and the between-study heterogeneity estimated was low (SD 0.14, 95% CrI 0.06 to 0.23). A random-class model with fixed-treatment effects was fitted, which improved fit compared to the fixed treatment with fixed-class effects model. However, we selected the random-treatment-effects model with a fixed-class as it had the lowest DIC.

The inconsistency model with random-treatment effects and fixed-class effects did not show an improvement in fit or a reduction in the between-study heterogeneity compared to the selected NMA model assuming consistency, suggesting no evidence of inconsistency.

Plotting each data point's contribution to the residual deviance in the NMA and inconsistency models did not show substantial improvement in fit for any data points (Figure 25c). Reported results are therefore based on the random-treatment-effects NMA model with fixed-class effects (assuming consistency).

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	380.57	0.14 (0.06 to 0.23)	46.38
Fixed-effect model	391.67		70.62
Random-effects inconsistency model	383.65	0.13 (0.05 to 0.22)	47.95
Random-class-effects models			
Fixed-effect model	385.45		53.20

[a] compare to 47 data points

Outcome: change from baseline in St George's Respiratory Questionnaire score at 3 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was low (SD 0.19, 95% CrI 0.006 to 0.67). We chose the fixed-treatment-effect model as it had the lowest DIC. The inconsistency model with fixed-treatment effects did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA (consistency), and inconsistency models, which showed an equal or better fit of points in the consistency model compared to the inconsistency model (Figure 27c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	170.91	0.19 (0.006 to 0.67)	43.82
Fixed-effect model	169.00		43.55
Fixed-effect inconsistency model	174.43		45.99

[a] compare to 59 data points

Outcome: change from baseline in St George's Respiratory Questionnaire score at 6 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was moderate to low (SD 0.36, 95% CrI 0.17 to 1.08). We chose the fixed-treatment-effect model as it had the lowest DIC.

The inconsistency model with fixed-treatment effects did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA (consistency), and inconsistency models, which showed no improvement in fit for any points in the inconsistency model (Figure 28c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	149.50	0.36 (0.17 to 1.08)	45.83
Fixed-effect model	148.02		48.20
Fixed-effect inconsistency model	151.37		49.56

[a] compare to 47 data points

Outcome: change from baseline in St George's Respiratory Questionnaire score at 12 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was moderate (SD 0.61, 95% CrI 0.29 to 2.51). We chose the fixed-treatment-effect model as it had the lowest DIC.

The inconsistency model with fixed-treatment effects did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA and inconsistency models, which showed an equal or better fit of points in the consistency model compared to the inconsistency model (Figure 29c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	42.48	0.61 (0.29 to 2.51)	14.22
Fixed-effect model	41.25		15.09
Fixed-effect inconsistency model	43.24		16.07

[a] compare to 15 data points

Outcome: Transition Dyspnoea Index at 3 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The random-effects model had a better fit than the fixed-effect model with a lower DIC and the between-study heterogeneity was moderate (SD 0.17, 95% CrI 0.02 to 0.32). We fitted a random-class model with fixed-treatment effects, which improved fit substantially compared to the fixed-treatment-effect models with a fixed-class but only slightly compared to the random-treatment-effects model with a fixed-class. As there were not enough data to estimate the within-class variance for the LABA/ICS group, we assumed that this was equal to the variance in the other combination therapy group (LABA/LAMA).

DIC slightly favoured the fixed-treatment-effect model with a random-class over the random-treatment-effects model with a fixed-class (difference of 3.6 points, which is close to the value for no meaningful difference). Within-class variability in the fixed-treatment-effect model with random-class was moderate (Table 71). We chose the random-treatment-effects model with a fixed-class as it is more interpretable. However, there is statistical uncertainty as to whether the variability observed across treatment effects is due to between-study or within-class/group differences.

The inconsistency model with random-treatment effects and fixed-class did not show an improvement in fit or reduction in heterogeneity compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA and inconsistency models, which showed no substantial improvement in fit of any points in the inconsistency model (Figure 31c).

Reported results are based on the random-treatment-effects model with fixed-class NMA model (assuming consistency), with the results for the fixed-treatment-effect model with random-class also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	14.34	0.17 (0.02 to 0.32)	61.72
Fixed-effect model	17.97		75.50
Random-effects inconsistency model	18.29	0.19 (0.04 to 0.35)	62.33
Random-class-effects models			
Fixed-effect model	10.71		59.48

[a] compare to 63 data points

Outcome: Transition Dyspnoea Index at 6 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was low (SD 0.09, 95% CrI 0.004 0 0.24). We chose the fixed-treatment-effect model as it had the lowest DIC.

The inconsistency model with fixed-treatment effects did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. Plotting each data point's contribution to the residual deviance in the NMA and inconsistency models, showed only a small improvement in fit for some points in the inconsistency model compared to the consistency model (Figure 32c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-classes are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	2.31	0.09 (0.004 to 0.24)	36.56

(*Continued)*

Fixed-effect model	0.59		37.73
Fixed-effect inconsistency model	2.08		37.24

[a]compare to 41 data points

Outcome: Transition Dyspnoea Index at 12 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The random-effects model had a better fit than the fixed-effect model although their DIC was comparable and between-study heterogeneity was moderate (SD 0.16, 95% CrI 0.02 to 0.43). We fitted a random-class model with fixed-treatment effects, which improved fit compared to the fixed-treatment-effect model with a fixed-class although with a similar DIC. Since all models had similar DIC, we chose the fixed-treatment-effect model with a fixed-class, as it is the simplest.

The inconsistency model with fixed-treatment effects (and fixed-class), did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA and inconsistency models, which showed an equal or better fit of points in the consistency model compared to the inconsistency model (Figure 33c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects assuming consistency. Results based on the random-treatment-effects model with fixed-classes are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	-6.91	0.16 (0.01 to 0.43)	14.19
Fixed-effect model	-5.15		19.59
Fixed-effect inconsistency model	-5.15		19.59
Random-class-effects models			
Fixed-effect model	-5.04		15.06

[a]compare to 16 data points

Outcome: change from baseline in forced expiratory volume in 1 second at 3 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The random-effects model had a better fit than the fixed-effect model with a lower DIC and the between-study heterogeneity was moderate (SD 0.03, 95% CrI 0.02 to 0.03). A random-class model with fixed-treatment effects was fitted which improved fit compared to the fixed-treatment-effect model with a fixed-class. However, the random-treatment-effects model with a fixed-class was selected as it had the lowest DIC.

The inconsistency model with random-treatment effects (and fixed-class) did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA and inconsistency models, which showed no substantial improvement in the fit of points in the inconsistency model (Figure 35c).

Reported results are therefore based on the random-effects NMA model with fixed-classes (assuming consistency).

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	-513.575	0.03 (0.02 to 0.03)	105.6
Fixed-effect model	-421.49		229.0
Random-effects inconsistency model	-514.67	0.02 (0.02 to 0.03)	104.4
Random-class-effects models			
Fixed-effect model	-481.10		155.2

[a] compare to 107 data points

Outcome: change from baseline in forced expiratory volume in 1 second at 6 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The random-effects model had a better fit than the fixed-effect model with a lower DIC and the between-study heterogeneity was moderate (SD 0.02, 95% CrI 0.007 to 0.03). We fitted a random-class model with fixed-treatment effects, which improved fit substantially compared to the fixed-treatment-effect models with a fixed-class but not compared to the random-treatment-effects model with a fixed-class. As there were not enough data to estimate the within-class variance for the LABA/ICS group, we assumed that this was equal to the variance in the other combination therapy group (LABA/LAMA).

The difference in DIC between the fixed-treatment-effect model with a random-class and the random-treatment-effects model with a fixed-class was less than 3 points. Within-class variability in the fixed-treatment-effect model with random-class was moderate. We chose the random-treatment-effects model with a fixed-class as it is more interpretable. However, there is statistical uncertainty as to whether the variability observed across treatment effects is due to between-study or within-class differences.

The inconsistency model with random-treatment effects (and fixed-class) showed some improvement in fit compared to the NMA model assuming consistency and had lower between-study heterogeneity and DIC, suggesting some evidence of inconsistency. Plotting each data point's contribution to the residual deviance in the NMA and inconsistency models showed that fit improved for some studies in the inconsistency model compared to the consistency models, although for other studies fit was worse (Figure 36c).

Reported results are based on the random-treatment-effects model with fixed-class NMA model (assuming consistency) with the results for the fixed-treatment-effect model with random-class also reported for comparison. However, there is weak evidence of potential inconsistency in this network and results should be interpreted with some caution.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	-324.38	0.02 (0.007 to 0.03)	68.26
Fixed-effect model	-315.31		91.40
Random-effects inconsistency model	-328.14	0.01 (0.000 to 0.02)	66.91

(*Continued*)

Random-class-effects models			
Fixed-effect model	-326.62		68.99

[a] compare to 69 data points

Within class/group standard deviation for change from baseline in FEV1 at 6 months in the low-risk population

Fixed-treatment-effect model with random-class

	Median	95% CrI
LABA	0.010	(0.000 to 0.052)
LAMA	0.020	(0.003 to 0.064)
LABA/ICS	0.025	(0.009 to 0.068)
LABA/LAMA	0.025	(0.009 to 0.068)

Outcome: change from baseline in forced expiratory volume in 1 second at 12 months

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The random-effects model had a better fit than the fixed-effect model with a lower DIC and the between-study heterogeneity was moderate (SD 0.02, 95% CrI 0.01 to 0.04). We fitted a random-class model with fixed-treatment effects, which improved fit compared to the fixed-treatment-effect model with a fixed-class. DIC was lower in the model with fixed-treatment and random-class effects, although there was evidence of overfitting. We therefore report results for both the random-treatment-effects model with a fixed-class and the fixed-treatment-effect model with a random-class (Table 60). Within-class variability in the fixed-treatment-effect model with random-class was moderate. There is some evidence that the variability observed across treatment effects may be due to within-class/group differences rather than between-study heterogeneity. The inconsistency model with random-treatment effects and fixed-class had an improved model fit and lower between-study heterogeneity and DIC when compared to the equivalent consistency model.

The inconsistency model with fixed-treatment effects with random-class did not show an improvement in fit or DIC when compared to the equivalent consistency model therefore suggesting no evidence of inconsistency. Plotting each data point's contribution to the residual deviance in the NMA and inconsistency models confirmed this (Figure 37c).

Reported results are based on the fixed-treatment-effect NMA model with random-classes (assuming consistency), with the results for the random-treatment-effects model with fixed-classes also reported for comparison. However, there is weak evidence of potential inconsistency in the latter model so results should be interpreted with caution.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	−150.21	0.02 (0.01 to 0.04)	32.70

(*Continued*)

Fixed-effect model	−142.19		49.03
Random-effects inconsistency model	−154.87	0.01 (0.00 to 0.03)	29.46
Random-class-effects models			
Fixed-effect model	−155.96		27.93
Fixed-effect inconsistency model	−154.3		28.87

[a]compare to 31 data points

Within class/group standard deviation for change from baseline in FEV1 at 12 months in the low-risk population

Fixed-treatment-effect model with random-class

	Median	**95% CrI**
LABA	0.019	(0.001 to 0.422)
LAMA	0.018	(0.004 to 0.073)
LABA/LAMA	0.045	(0.016 to 0.158)

Outcome: mortality

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The posterior mean of the residual deviance was substantially larger than the number of data points for both models and the between-study heterogeneity was moderate (SD 0.15, 95% CrI 0.007 to 0.70). We considered random-class models with fixed- and random-treatment effects but this only slightly improved fit compared to the fixed-class models. The fixed-treatment-effect model with fixed-class had the lowest DIC so we chose this model.

The inconsistency model with fixed-treatment effects (and fixed-class) showed no improvement in fit or DIC compared to the NMA model assuming consistency, suggesting no evidence of inconsistency (Figure 39c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison. Results should be interpreted with some caution due to poor model fit which can be attributed to studies with zero cells.

	DIC	**SD (95% CrI)**	**Total residual deviance**[a]
Fixed-class-effect models			
Random-effects model	432.52	0.15 (0.007 to 0.70)	129.4

(*Continued)*

Fixed-effect model	430.85		131.9
Fixed-effect inconsistency model	430.73		132.4
Random-class-effects models			
Fixed-effect model	435.98		134.5

[a] compare to 110 data points

Outcome: total serious adverse events

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. Both models fitted the data well and between-study heterogeneity was low (SD 0.04, 95% CrI 0.00 to 0.15). We chose the fixed-effect model as it had the lowest DIC.
The inconsistency model with fixed-treatment effects (and fixed-class effects) did not show an improvement in fit compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA and inconsistency models, which showed no improvement in fit for any data point (Figure 40c).
Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	891.21	0.04 (0 to 0.15)	145.8
Fixed-effect model	889.36		147.7
Fixed-effect inconsistency	894.82		150.2

[a] compare to 145 data points

Outcome: chronic obstructive pulmonary disease serious adverse events

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The posterior mean of the residual deviance was substantially larger than the number of data points for both models and the between-study heterogeneity was moderate (SD 0.16, 95% CrI 0.002 to 0.38). Random-class models with fixed- and random-treatment effects were fitted and although model fit was improved the fixed-class models had lower DIC. The fixed-treatment-effect model with fixed-class had the lowest DIC so we chose this model.
The inconsistency model with fixed-treatment effects (and fixed-class) showed no improvement in fit or DIC compared to the NMA model assuming consistency, suggesting no evidence of inconsistency (Figure 41c). However, plotting each data point's contribution to the residual deviance in the NMA and inconsistency models there were a few studies with slightly improved fit in the inconsistency, compared to the consistency model, suggesting some evidence of inconsistency (Figure 41c).
Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison. Results should be interpreted with some caution due to poor model fit, which can be attributed to studies with zero cells.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	662.62	0.16 (0.002 to 0.38)	144.2
Fixed-effect model	661.91		151.0
Fixed-effect inconsistency	666.00		152.4
Random-class-effects models			
Random-effects model	665.07	0.13 (0.006 to 0.37)	140.1
Fixed-effect model	664.86		143.9

[a] compare to 135 data points

Outcome: cardiac serious adverse events

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. The posterior mean of the residual deviance was substantially larger than the number of data points for both models and the between-study heterogeneity was moderate (SD 0.16, 95% CrI 0.006 to 0.48). We fitted random-class models with fixed- and random-treatment effects and although model fit was improved the fixed-class models had lower DIC. The fixed-treatment-effect model with fixed-class had the lowest DIC so we chose this model.
The inconsistency model with fixed-treatment effects (and fixed-class) showed some improvement in fit or DIC compared to the NMA model assuming consistency, suggesting evidence of inconsistency. Plotting each data point's contribution to the residual deviance in the NMA and inconsistency models showed improved fit for one study in the inconsistency model, suggesting some evidence of inconsistency (Figure 42c). Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison. Results should be interpreted with some caution due to poor model fit, which can be attributed to studies with zero cells.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	578.42	0.17 (0.006 to 0.48)	151.2
Fixed-effect model	577.25		155.8
Fixed-effect inconsistency	572.69		149.3
Random-class-effects models			
Random-effects model	581.73	0.16 (0.008 to 0.49)	147.0
Fixed-effect model	581.40		150.5

[a] compare to 127 data points

Outcome: dropouts due to adverse events

We fitted random- and fixed-treatment-effect NMA models with fixed-class effects. The posterior mean of the residual deviance was substantially larger than the number of data points for both models and the between-study heterogeneity was low (SD 0.09, 95% CrI 0.004 to 0.24). Random-class models with fixed- and random-treatment effects were fitted and although model fit was improved the DIC was comparable to the fixed-class models. The fixed-treatment-effect model with fixed-class had the lowest DIC so we chose this model.

The inconsistency model with fixed-treatment effects (and fixed-class) showed no improvement in fit or DIC compared to the NMA model assuming consistency, suggesting no evidence of inconsistency. We confirmed this by plotting each data point's contribution to the residual deviance in the NMA and inconsistency models, where fit was the same or better for the consistency model for most data points (Figure 43c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class are also reported for comparison. Results should be interpreted with some caution due to poor model fit.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	848.0	0.09 (0.004 to 0.24)	155.6
Fixed-effect model	846.7		160.5
Fixed-effect inconsistency	849.3		160.2
Random-class-effects models			
Random-effects model	847.3	0.09 (0.003 to 0.23)	144.8
Fixed-effect model	846.9		148.6

[a] compare to 146 data points

Outcome: pneumonia

We fitted random- and fixed-treatment-effects NMA models with fixed-class effects. There was some evidence that the posterior distribution of the between-study heterogeneity was poorly estimated so we used an informative prior distribution, based on Turner 2012. We selected the prior distribution suggested for the between-study variance of a subjective outcome (infection, new disease), for comparisons of pharmacological interventions.

The random-effects model had a better fit than the fixed-effect model with a lower DIC although the posterior mean of the residual deviance was still considerably larger than the number of data points and the between-study heterogeneity was moderate (SD 0.23, 95% CrI 0.05 to 0.65). We fitted random-class models with fixed- and random-treatment effects, which improved fit slightly compared to the fixed-class model. However, DIC was lowest for the fixed-treatment-effect model with a fixed-class so we chose this model.

The inconsistency models with fixed-treatment effects (and fixed-class) showed an improvement in fit and DIC compared to the NMA model assuming consistency, suggesting some evidence of inconsistency.

Plotting each data point's contribution to the residual deviance in the NMA and inconsistency models, there was some improvement in fit for a few studies in the inconsistency model although most of the studies with high residual deviance contained zero-event arms, of which there were many in the dataset (Figure 44c).

Reported results are therefore based on the fixed-treatment-effect NMA model with fixed-class effects, assuming consistency. Results based on the random-treatment-effects model with fixed-class and informative prior distribution on the heterogeneity parameter are also reported for comparison. Results should be interpreted with caution due to potential inconsistency in the data.

	DIC	SD (95% CrI)	Total residual deviance[a]
Fixed-class-effect models			
Random-effects model	531.76	0.23 (0.05 to 0.65)	167.3
Fixed-effect model	532.14		174.3
Fixed-effect inconsistency model	525.77		166.0
Random-class-effects models			
Random-effects model	531.13	0.22 (0.05 to 0.61)	158.4
Fixed-effect model	531.66		162.0

[a] compare to 133 data points
DIC: deviance information criterion; **SD:** standard deviation

Appendix 5. Ranking summary

Outcome	Treatment group	High-risk population			Low-risk population		
		Mean	Median	95% CrI	Mean	Median	95% CrI
Moderate to severe exacerbations	LABA/LAMA	1	1	(1 to 2)	1.1	1	(1 to 2)
	LAMA	2.4	2	(2 to 3)	2.2	2	(1 to 3)
	LABA/ICS	2.6	3	(2 to 3)	2.6	3	(2 to 3)
	LABA	4	4	(4 to 4)	4	4	(4 to 4)
Severe exacerbations	LABA/LAMA	1.2	1	(1 to 2)	1.3	1	(1 to 3)
	LAMA	1.9	2	(1 to 3)	1.9	2	(1 to 3)
	LABA/ICS	3	3	(2 to 3)	3.3	3	(2 to 4)
	LABA	4	4	(4 to 4)	3.5	4	(2 to 4)
SGRQ responders at 3 months	LABA	NA	NA	NA	1.4	1	(1 to 3)
	LABA/LAMA	NA	NA	NA	1.8	2	(1 to 3)
	LABA/ICS	NA	NA	NA	2.8	3	(1 to 3)

(*Continued*)

	LAMA	NA	NA	NA	4	4	(4 to 4)
SGRQ responders at 6 months	LABA/LAMA	NA	NA	NA	1	1	(1 to 2)
	LABA/ICS	NA	NA	NA	2.7	2	(1 to 4)
	LAMA	NA	NA	NA	3	3	(2 to 4)
	LABA	NA	NA	NA	3.3	3	(2 to 4)
SGRQ score at 3 months	LABA/LAMA	1	1	(1 to 1)	1.7	2	(1 to 3)
	LABA/ICS	2	2	(2 to 2)	1.6	2	(1 to 3)
	LABA	3.4	3	(3 to 4)	2.8	3	(1 to 4)
	LAMA	3.6	4	(3 to 4)	3.9	4	(3 to 4)
SGRQ score at 6 months	LABA/LAMA	1	1	(1 to 1)	1.3	1	(1 to 2)
	LABA/ICS	2	2	(2 to 2)	1.7	2	(1 to 3)
	LAMA	3.2	3	(3 to 4)	3.3	3	(2 to 4)
	LABA	3.8	4	(3 to 4)	3.7	4	(3 to 4)
SGRQ score at 12 months	LABA/LAMA	1.1	1	(1 to 2)	2	2	(1 to 3)
	LABA/ICS	2	2	(1 to 3)	1.1	1	(1 to 2)
	LAMA	2.9	3	(2 to 3)	3.3	3	(2 to 4)
	LABA	4	4	(4 to 4)	3.6	4	(3 to 4)
TDI at 3 months	LABA/LAMA	NA	NA	NA	1	1	(1 to 1)
	LABA/ICS	NA	NA	NA	2.3	2	(2 to 4)
	LABA	NA	NA	NA	3	3	(2 to 4)
	LAMA	NA	NA	NA	3.7	4	(2 to 4)
TDI at 6 months	LABA/LAMA	NA	NA	NA	1.1	1	(1 to 2)
	LABA/ICS	NA	NA	NA	2	2	(1 to 4)
	LAMA	NA	NA	NA	3.2	3	(2 to 4)
	LABA	NA	NA	NA	3.6	4	(3 to 4)

(*Continued*)

TDI at 12 months	LABA/LAMA	NA	NA	NA	1	1	(1 to 1)
	LAMA	NA	NA	NA	2.06	2	(2 to 3)
	LABA	NA	NA	NA	2.94	3	(2 to 3)
	LABA/ICS	NA	NA	NA	NA	NA	NA
FEV1 at 3 months	LABA/LAMA	1	1	(1 to 1)	1	1	(1 to 1)
	LABA/ICS	2.4	2	(2 to 3)	2	2	(2 to 2)
	LAMA	2.6	3	(2 to 3)	3.2	3	(3 to 4)
	LABA	4	4	(4 to 4)	3.8	4	(3 to 4)
FEV1 at 6 months	LABA/LAMA	1	1	(1 to 1)	1	1	(1 to 1)
	LAMA	2.1	2	(2 to 3)	2.7	3	(2 to 4)
	LABA/ICS	2.9	3	(2 to 3)	2.3	2	(2 to 4)
	LABA	4	4	(4 to 4)	3.9	4	(3 to 4)
FEV1 at 12 months	LABA/LAMA	1	1	(1 to 1)	1.1	1	(1 to 2)
	LAMA	2	2	(2 to 2)	2	2	(1 to 3)
	LABA/ICS	3	3	(3 to 3)	NA	NA	NA
	LABA	4	4	(4 to 4)	3	3	(2 to 3)
Mortality	LABA/ICS	1.6	1	(1 to 4)	1.5	1	(1 to 4)
	LABA/LAMA	2.6	3	(1 to 4)	3	3	(1 to 4)
	LAMA	2.8	3	(1 to 4)	3.5	4	(1 to 4)
	LABA	3	3	(1 to 4)	2.1	2	(1 to 4)
Dropouts due to adverse event	LABA/LAMA	1.6	1	(1 to 4)	2.5	2	(1 to 4)
	LAMA	2.2	2	(1 to 4)	1.3	1	(1 to 3)
	LABA/ICS	2.4	2	(1 to 4)	2.5	3	(1 to 4)
	LABA	3.9	4	(3 to 4)	3.7	4	(2 to 4)
Pneumonia	LAMA	1.5	1	(1 to 3)	1.6	1	(1 to 3)

(*Continued*)

	LABA/LAMA	1.9	2	(1 to 3)	2.7	3	(1 to 4)
	LABA	2.6	3	(1 to 3)	1.8	2	(1 to 3)
	LABA/ICS	4	4	(4 to 4)	4	4	(3 to 4)

FEV1: forced expiratory volume in one second;**ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **NA:** not applicable; **SGRQ:** St George's Respiratory Questionnaire; **TDI:** Transition Dyspnoea Index

Appendix 6. Summary of results for pairwise and network meta-analyses in the high-risk population

Moderate to severe exacerbations, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA (random-effects/ fixed-class) HR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	0.87 (0.76 to 1.00)	0.87 (0.76 to 1.00)	0.86 (0.76 to 0.99)
LABA/LAMA vs LAMA	Moderate	1.06 (0.89 to 1.27)	1.06 (0.89 to 1.27)	0.87 (0.78 to 0.99)
LABA/LAMA vs LABA	NA	NA	NA	0.70 (0.61 to 0.80)
LABA/ICS vs LAMA	Moderate	1.12 (0.90 to 1.39)	1.12 (0.90 to 1.39)	1.01 (0.91 to 1.13)
LABA/ICS vs LABA	High	0.81 (0.75 to 0.89)	0.81 (0.75 to 0.89)	0.80 (0.75 to 0.86)
LAMA vs LABA	High	0.84 (0.76 to 0.92)	0.84 (0.76 to 0.92)	0.80 (0.71 to 0.88)
Severe exacerbations, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(fixed-effect/ fixed-class) HR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	0.88 (0.74 to 1.06)	0.88 (0.74 to 1.06)	0.78 (0.64 to 0.93)
LABA/LAMA vs LAMA	Moderate	0.73 (0.45 to 1.16)	0.73 (0.45 to 1.16)	0.89 (0.71 to 1.11)
LABA/LAMA vs LABA	NA	NA	NA	0.64 (0.51 to 0.81)
LABA/ICS vs LAMA	Moderate	1.28 (0.95 to 1.73)	1.28 (0.95 to 1.73)	1.15 (0.97 to 1.36)
LABA/ICS vs LABA	Moderate	0.91 (0.74 to 1.13)	0.91 (0.74 to 1.12)	0.83 (0.71 to 0.97)
LAMA vs LABA	Moderate	0.88 (0.78 to 1.01)	0.88 (0.78 to 1.01)	0.72 (0.63 to 0.82)

(*Continued*)

SGRQ responders at 3 months, high-risk	Certainty of evidence in the pairwise MA	Pairwise, random-effects OR (95% CI)	Pairwise, fixed-effect OR (95% CI)	NMA(fixed-effect/ fixed-class) MD (95% CrI)
LABA/LAMA vs LABA/ ICS	NA	NA	NA	NA
LABA/LAMA vs LAMA	NA	NA	NA	NA
LABA/LAMA vs LABA	NA	NA	NA	NA
LABA/ICS vs LAMA	Low	0.96 (0.56 to 1.65)	0.96 (0.56 to 1.65)	NA
LABA/ICS vs LABA	NA	NA	NA	NA
LAMA vs LABA	Moderate	0.97 (0.84 to 1.12)	0.97 (0.84 to 1.12)	NA
SGRQ responders at 6 months, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(random-effects/ fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ ICS	NA	NA	NA	NA
LABA/LAMA vs LAMA	Moderate	1.30 (1.08 to 1.56)	1.30 (1.08 to 1.56)	NA
LABA/LAMA vs LABA	NA	NA	NA	NA
LABA/ICS vs LAMA	Moderate	1.26 (0.99 to 1.59)	1.26 (0.99 to 1.59)	NA
LABA/ICS vs LABA	NA	NA	NA	NA
LAMA vs LABA	Low	1.08 (0.93 to 1.25)	1.08 (0.93 to 1.25)	NA
SGRQ responders at 12 months, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(fixed-effect/ fixed-class) OR (95% CrI)**
LABA/LAMA vs LABA/ ICS	High	1.25 (1.09 to 1.43)	1.25 (1.09 to 1.43)	1.21 (1.07 to 1.36)
LABA/LAMA vs LAMA	Low	1.27 (1.04 to 1.55)	1.27 (1.04 to 1.55)	1.36 (1.18 to 1.58)
LABA/LAMA vs LABA	NA	NA	NA	1.41 (1.2 to 1.66)
LABA/ICS vs LAMA	Moderate	1.15 (0.90 to 1.47)	1.15 (0.90 to 1.47)	1.13 (0.98 to 1.3)
LABA/ICS vs LABA	Moderate	1.15 (0.78 to 1.72)	1.22 (1.03 to 1.46)	1.17 (1.02 to 1.34)

(*Continued*)

LAMA vs LABA	Moderate	1.00 (0.86 to 1.17)	1.00 (0.86 to 1.17)	1.03 (0.91 to 1.18)
CFB in SGRQ at 3 months, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD(95% CI)**	**Pairwise, fixed-effect MD(95% CI)**	**NMA(fixed-effect/ fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ ICS	High	−1.30 (−2.35 to −0. 25)	−1.30 (−2.35 to −0. 25)	−1.39 (−2.37 to −0. 42)
LABA/LAMA vs LAMA	Moderate	-3.68 (-5.84 to −1.52)	-3.68 (-5.84 to −1.52)	-3.31 (-4.67 to −1.97)
LABA/LAMA vs LABA	NA	NA	NA	-3.21 (-4.52 to −1.92)
LABA/ICS vs LAMA	Low	−1.06 (-4.39 to 2.27)	−1.06 (-4.39 to 2.27)	−1.92 (-3.11 to −0.74)
LABA/ICS vs LABA	Low	−1.81 (−2.99 to −0. 64)	−1.81 (−2.99 to −0. 64)	−1.82 (−2.86 to −0. 78)
LAMA vs LABA	High	0.10 (−0.82 to 1.02)	0.10 (−0.82 to 1.02)	0.10 (−0.76 to 0.96)
CFB in SGRQ at 6 months, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD(95% CI)**	**Pairwise, fixed-effect MD(95% CI)**	**NMA(fixed-effect/ fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ ICS	High	−1.20 (−2.28 to −0. 12)	−1.20 (−2.28 to −0. 12)	−1.27 (−2.26 to −0. 29)
LABA/LAMA vs LAMA	Moderate	−2.79 (-5.02 to −0.56)	−2.79 (-5.02 to −0.56)	−2.48 (-3.72 to −1.24)
LABA/LAMA vs LABA	NA	NA	NA	−2.88 (-4.03 to −1.73)
LABA/ICS vs LAMA	Low	−1.97 (-3.79 to −0.15)	−1.97 (-3.79 to −0.15)	−1.21 (−2.16 to −0. 25)
LABA/ICS vs LABA	Very low	−1.40 (−2.53 to −0. 26)	−1.45 (−2.17 to −0. 73)	−1.6 (−2.27 to −0.93)
LAMA vs LABA	High	−0.70 (−1.74 to 0.34)	−0.70 (−1.74 to 0.34)	−0.39 (−1.27 to 0.47)
CFB in SGRQ at 12 months, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD(95% CI)**	**Pairwise, fixed-effect MD(95% CI)**	**NMA(fixed-effect/ fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ ICS	High	−1.20 (−2.34 to −0. 06)	−1.20 (−2.34 to −0. 06)	−0.52 (−1.42 to 0.36)
LABA/LAMA vs LAMA	Low	-3.38 (-5.83 to −0.93)	-3.38 (-5.83 to −0.93)	−1.12 (−1.88 to −0. 37)

(*Continued*)

LABA/LAMA vs LABA	NA	NA	NA	−2.1 (-3.08 to −1.13)
LABA/ICS vs LAMA	Low	−0.99 (−2.98 to 1.00)	−0.99 (−2.98 to 1.00)	−0.59 (−1.48 to 0.29)
LABA/ICS vs LABA	Moderate	−1.75 (−2.61 to −0.89)	−1.78 (−2.49 to −1.07)	−1.57 (−2.23 to −0.92)
LAMA vs LABA	High	−0.40 (−1.56 to 0.76)	−0.40 (−1.56 to 0.76)	−0.98 (−1.86 to −0.08)
TDI at 3 months, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD(95% CI)**	**Pairwise, fixed-effect MD(95% CI)**	**NMA**
LABA/LAMA vs LABA/ICS	NA	NA	NA	NA
LABA/LAMA vs LAMA	NA	NA	NA	NA
LABA/LAMA vs LABA	NA	NA	NA	NA
LABA/ICS vs LAMA	Moderate	0.50 (0.18 to 0.82)	0.50 (0.18 to 0.82)	NA
LABA/ICS vs LABA	NA	NA	NA	NA
LAMA vs LABA	Moderate	−0.14 (−0.15 to −0.13)	−0.14 (−0.15 to −0.13)	NA
TDI at 6 months, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD(95% CI)**	**Pairwise, fixed-effect MD(95% CI)**	**NMA**
LABA/LAMA vs LABA/ICS	NA	NA	NA	NA
LABA/LAMA vs LAMA	NA	NA	NA	NA
LABA/LAMA vs LABA	NA	NA	NA	NA
LABA/ICS vs LAMA	Moderate	0.30 (−0.06 to 0.66)	0.30 (−0.06 to 0.66)	NA
LABA/ICS vs LABA	NA	NA	NA	NA
LAMA vs LABA	Moderate	−0.19 (−0.20 to −0.18)	−0.19 (−0.20 to −0.18)	NA
TDI at 12 months, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD(95% CI)**	**Pairwise, fixed-effect MD(95% CI)**	**NMA**

(*Continued*)

LABA/LAMA vs LABA/ICS	NA	NA	NA	NA
LABA/LAMA vs LAMA	Moderate	−0.38 (−1.28 to 0.52)	−0.38 (−1.28 to 0.52)	NA
LABA/LAMA vs LABA	NA	NA	NA	NA
LABA/ICS vs LAMA	Low	0.00 (−0.40 to 0.40)	0.00 (−0.40 to 0.40)	NA
LABA/ICS vs LABA	NA	NA	NA	NA
LAMA vs LABA	Moderate	−0.26 (−0.27 to −0.25)	−0.26 (−0.27 to −0.25)	NA
CFB in FEV1 at 3 months, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD(95% CI)**	**Pairwise, fixed-effect MD(95% CI)**	**NMA(fixed-effect/fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ICS	High	0.08 (0.06 to 0.10)	0.08 (0.06 to 0.10)	0.07 (0.05 to 0.09)
LABA/LAMA vs LAMA	Moderate	0.06 (0.02 to 0.09)	0.06 (0.02 to 0.09)	0.07 (0.05 to 0.10)
LABA/LAMA vs LABA	NA	NA	NA	0.12 (0.10 to 0.15)
LABA/ICS vs LAMA	High	0.01 (−0.02 to 0.04)	0.01 (−0.02 to 0.03)	0.00 (−0.02 to 0.02)
LABA/ICS vs LABA	Moderate	0.05 (0.03 to 0.07)	0.05 (0.04 to 0.07)	0.05 (0.04 to 0.07)
LAMA vs LABA	NA	NA	NA	0.05 (0.02 to 0.07)
CFB in FEV1 at 6 months, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD(95% CI)**	**Pairwise, fixed-effect MD(95% CI)**	**NMA(fixed-effect/fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ICS	High	0.09 (0.07 to 0.11)	0.09 (0.07 to 0.11)	0.08 (0.06 to 0.10)
LABA/LAMA vs LAMA	Moderate	0.06 (0.02 to 0.10)	0.06 (0.02 to 0.10)	0.07 (0.04 to 0.09)
LABA/LAMA vs LABA	NA	NA	NA	0.13 (0.10 to 0.15)
LABA/ICS vs LAMA	Moderate	−0.01 (−0.04 to 0.02)	−0.01 (−0.04 to 0.02)	−0.02 (−0.04 to 0.01)
LABA/ICS vs LABA	Moderate	0.05 (0.03 to 0.07)	0.04 (0.03 to 0.06)	0.04 (0.03 to 0.06)
LAMA vs LABA	NA	NA	NA	0.06 (0.03 to 0.08)

(*Continued*)

CFB in FEV1 at 12 months, high-risk	Certainty of evidence in the pairwise MA	Pairwise, random-effects MD(95% CI)	Pairwise, fixed-effect MD(95% CI)	NMA (random-effects/ fixed-class) MD (95% CrI)
LABA/LAMA vs LABA/ ICS	Moderate	0.06 (0.04 to 0.08)	0.06 (0.04 to 0.08)	0.07 (0.04 to 0.1)
LABA/LAMA vs LAMA	Moderate	0.05 (0.01 to 0.09)	0.05 (0.01 to 0.09)	0.04 (0 to 0.08)
LABA/LAMA vs LABA	NA	NA	NA	0.12 (0.08 to 0.16)
LABA/ICS vs LAMA	Very low	−0.01 (−0.08 to 0.05)	−0.03 (−0.06 to 0.00)	−0.03 (−0.07 to 0.01)
LABA/ICS vs LABA	Moderate	0.05 (0.03 to 0.07)	0.04 (0.03 to 0.06)	0.05 (0.03 to 0.07)
LAMA vs LABA	NA	NA	NA	0.08 (0.04 to 0.12)
Mortality, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(fixed-effect/ fixed-class) OR[a] (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	1.00 (0.57 to 1.77)	1.00 (0.57 to 1.77)	1.12 (0.75 to 1.68)
LABA/LAMA vs LAMA	Moderate	1.06 (0.66 to 1.69)	1.06 (0.66 to 1.69)	0.98 (0.66 to 1.42)
LABA/LAMA vs LABA	NA	NA	NA	0.97 (0.63 to 1.46)
LABA/ICS vs LAMA	Moderate	0.53 (0.31 to 0.90)	0.52 (0.31 to 0.89)	0.87 (0.65 to 1.16)
LABA/ICS vs LABA	Low	0.95 (0.69 to 1.30)	0.98 (0.73 to 1.33)	0.86 (0.66 to 1.11)
LAMA vs LABA	Moderate	0.87 (0.66 to 1.16)	0.87 (0.66 to 1.16)	0.99 (0.77 to 1.27)
Total SAEs, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(fixed-effect/ fixed-class) OR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	0.91 (0.76 to 1.08)	0.91 (0.76 to 1.08)	0.89 (0.77 to 1.02)
LABA/LAMA vs LAMA	Moderate	0.98 (0.80 to 1.20)	0.98 (0.80 to 1.20)	1.01 (0.87 to 1.17)
LABA/LAMA vs LABA	NA	NA	NA	0.89 (0.77 to 1.04)
LABA/ICS vs LAMA	Moderate	1.29 (1.03 to 1.63)	1.29 (1.03 to 1.63)	1.14 (1.02 to 1.27)
LABA/ICS vs LABA	High	0.99 (0.89 to 1.09)	0.99 (0.89 to 1.09)	1.01 (0.92 to 1.10)

(*Continued*)

LAMA vs LABA	Moderate	0.90 (0.81 to 1.00)	0.90 (0.81 to 1.00)	0.88 (0.81 to 0.97)
COPD SAEs high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(fixed-effect/ fixed-class) OR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	0.87 (0.70 to 1.07)	0.87 (0.70 to 1.07)	0.87 (0.73 to 1.04)
LABA/LAMA vs LAMA	Moderate	1.08 (0.84 to 1.39)	1.08 (0.84 to 1.39)	1.07 (0.89 to 1.28)
LABA/LAMA vs LABA	NA	NA	NA	0.82 (0.68 to 1.00)
LABA/ICS vs LAMA	Low	0.99 (0.33 to 2.96)	1.33 (0.99 to 1.79)	1.22 (1.05 to 1.42)
LABA/ICS vs LABA	Moderate	0.92 (0.78 to 1.07)	0.92 (0.79 to 1.07)	0.95 (0.83 to 1.08)
LAMA vs LABA	High	0.79 (0.69 to 0.91)	0.79 (0.69 to 0.91)	0.77 (0.68 to 0.87)
Cardiac SAEs, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(random-effects/ fixed-class) OR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	0.86 (0.58 to 1.29)	0.86 (0.58 to 1.29)	0.7 (0.03 to 5.88)
LABA/LAMA vs LAMA	Low	0.80 (0.53 to 1.20)	0.80 (0.53 to 1.20)	0.69 (0.02 to 25.46)
LABA/LAMA vs LABA	NA	NA	NA	0.83 (0.06 to 9.24)
LABA/ICS vs LAMA	Moderate	0.67 (0.39 to 1.15)	0.67 (0.39 to 1.15)	1.08 (0.06 to 23.81)
LABA/ICS vs LABA	Very low	0.97 (0.68 to 1.38)	0.96 (0.75 to 1.22)	1.27 (0.37 to 5.97)
LAMA vs LABA	Low	1.09 (0.83 to 1.44)	1.09 (0.84 to 1.43)	1.13 (0.06 to 21.22)
Dropouts due to AEs, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(random-effects/ fixed-class) OR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	0.88 (0.69 to 1.13)	0.88 (0.69 to 1.13)	0.93 (0.73 to 1.19)
LABA/LAMA vs LAMA	Low	1.03 (0.75 to 1.41)	1.03 (0.75 to 1.40)	0.95 (0.74 to 1.21)
LABA/LAMA vs LABA	NA	NA	NA	0.83 (0.65 to 1.07)
LABA/ICS vs LAMA	Moderate	1.04 (0.74 to 1.47)	1.04 (0.74 to 1.47)	1.02 (0.85 to 1.22)

(*Continued*)

LABA/ICS vs LABA	Low	0.88 (0.77 to 1.00)	0.88 (0.77 to 1.00)	0.89 (0.79 to 1.01)
LAMA vs LABA	High	0.91 (0.79 to 1.04)	0.91 (0.79 to 1.04)	0.88 (0.75 to 1.03)
Pneumonia, high-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(fixed-effect/ fixed-class)OR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	0.62 (0.40 to 0.96)	0.62 (0.40 to 0.96)	0.59 (0.41 to 0.83)
LABA/LAMA vs LAMA	Moderate	0.98 (0.59 to 1.61)	0.98 (0.60 to 1.61)	1.05 (0.72 to 1.5)
LABA/LAMA vs LABA	NA	NA	NA	0.88 (0.6 to 1.29)
LABA/ICS vs LAMA	Moderate	1.80 (1.06 to 3.06)	1.82 (1.07 to 3.09)	1.78 (1.33 to 2.39)
LABA/ICS vs LABA	Moderate	1.46 (1.03 to 2.08)	1.51 (1.14 to 1.99)	1.50 (1.17 to 1.92)
LAMA vs LABA	Moderate	0.83 (0.61 to 1.13)	0.83 (0.62 to 1.12)	0.84 (0.65 to 1.09)

[a]Potential inconsistency in the date. Results should be interpreted with caution
AE: adverse event; **CFB:** change from baseline; **HR:** hazard ratio; **FEV1:** forced expiratory volume in one second;**ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **MA:** meta-analysis; **MD:** mean difference; **NA:** not applicable; **NMA:** network meta-analysis; **OR:** odds ratio; **SAE:** serious adverse event; **SGRQ:** St George's Respiratory Questionnaire; **TDI:** Transition Dyspnoea Index

Appendix 7. Summary of results for pairwise and network meta-analyses in the low-risk population

Moderate to severe exacerbations, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(fixed-effect/ fixed-class) HR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	0.86 (0.65 to 1.14)	0.84 (0.68 to 1.06)	0.87 (0.75 to 1.01)
LABA/LAMA vs LAMA	Low	0.93 (0.66 to 1.30)	0.94 (0.78 to 1.14)	0.90 (0.76 to 1.06)
LABA/LAMA vs LABA	Moderate	0.77 (0.62 to 0.97)	0.77 (0.62 to 0.96)	0.78 (0.67 to 0.90)
LABA/ICS vs LAMA	Low	0.63 (0.24 to 1.66)	0.63 (0.24 to 1.66)	1.03 (0.91 to 1.17)
LABA/ICS vs LABA	Moderate	0.83 (0.70 to 0.98)	0.85 (0.76 to 0.95)	0.89 (0.84 to 0.96)
LAMA vs LABA	Moderate	0.92 (0.79 to 1.07)	0.92 (0.79 to 1.07)	0.87 (0.78 to 0.97)

(*Continued*)

Severe exacerbations, low-risk	Certainty of evidence in the pairwise MA	Pairwise, random-effects OR (95% CI)	Pairwise, fixed-effect OR (95% CI)	NMA(random-effects/ fixed-class) HR (95% CrI)
LABA/LAMA vs LABA/ ICS	Moderate	0.66 (0.27 to 1.63)	0.62 (0.33 to 1.19)	0.71 (0.47 to 1.08)
LABA/LAMA vs LAMA	Moderate	0.99 (0.57 to 1.72)	1.01 (0.65 to 1.55)	0.90 (0.6 to 1.31)
LABA/LAMA vs LABA	Moderate	0.78 (0.55 to 1.12)	0.78 (0.55 to 1.11)	0.72 (0.48 to 1.02)
LABA/ICS vs LAMA	Low	3.05 (0.32 to 29.47)	3.05 (0.32 to 29.47)	1.25 (0.86 to 1.85)
LABA/ICS vs LABA	High	1.06 (0.90 to 1.24)	1.06 (0.90 to 1.24)	1.01 (0.72 to 1.28)
LAMA vs LABA	Low	0.64 (0.36 to 1.13)	0.65 (0.41 to 1.03)	0.80 (0.56 to 1.05)
SGRQ responders at 3 months, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(fixed-effect/ fixed-class) OR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	1.08 (0.92 to 1.27)	1.08 (0.92 to 1.27)	1.07 (0.94 to 1.23)
LABA/LAMA vs LAMA	High	1.32 (1.16 to 1.51)	1.32 (1.17 to 1.49)	1.33 (1.19 to 1.48)
LABA/LAMA vs LABA	NA	NA	NA	0.96 (0.81 to 1.15)
LABA/ICS vs LAMA	Low	1.26 (0.92 to 1.74)	1.26 (0.92 to 1.74)	1.24 (1.07 to 1.43)
LABA/ICS vs LABA	Low	0.90 (0.73 to 1.11)	0.90 (0.73 to 1.11)	0.9 (0.76 to 1.06)
LAMA vs LABA	High	0.73 (0.59 to 0.89)	0.73 (0.59 to 0.89)	0.73 (0.62 to 0.85)
SGRQ responders at 6 months, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(random-effects/ fixed-class) OR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Low	1.29 (0.88 to 1.89)	1.29 (0.88 to 1.89)	1.22 (0.99 to 1.51)
LABA/LAMA vs LAMA	Moderate	1.26 (1.15 to 1.37)	1.26 (1.15 to 1.37)	1.26 (1.1 to 1.42)
LABA/LAMA vs LABA	Low	1.20 (1.06 to 1.37)	1.20 (1.06 to 1.37)	1.28 (1.11 to 1.47)
LABA/ICS vs LAMA	NA	NA	NA	1.03 (0.83 to 1.27)
LABA/ICS vs LABA	Moderate	1.08 (0.96 to 1.22)	1.08 (0.96 to 1.22)	1.05 (0.87 to 1.25)

(*Continued*)

LAMA vs LABA	Low	1.02 (0.89 to 1.16)	1.02 (0.93 to 1.11)	1.02 (0.9 to 1.16)
SGRQ responders at 12 months, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA**
LABA/LAMA vs LABA/ICS	NA	NA	NA	NA
LABA/LAMA vs LAMA	Moderate	1.13 (0.95 to 1.34)	1.13 (0.95 to 1.34)	NA
LABA/LAMA vs LABA	Moderate	1.19 (0.99 to 1.44)	1.19 (0.99 to 1.44)	NA
LABA/ICS vs LAMA	NA	NA	NA	NA
LABA/ICS vs LABA	Moderate	1.42 (1.18 to 1.70)	1.42 (1.18 to 1.70)	NA
LAMA vs LABA	Low	1.05 (0.88 to 1.26)	1.05 (0.88 to 1.26)	NA
CFB in SGRQ at 3 months, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD (95% CI)**	**Pairwise, fixed-effect MD (95% CI)**	**NMA(fixed-effect/ fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ICS	High	−0.03 (−1.02 to 0.96)	−0.03 (−1.02 to 0.96)	0.04 (−0.79 to 0.88)
LABA/LAMA vs LAMA	Moderate	−1.60 (−2.19 to −1.01)	−1.60 (−2.19 to −1.01)	−1.64 (−2.2 to −1.08)
LABA/LAMA vs LABA	Moderate	−1.29 (-4.29 to 1.71)	−1.29 (-4.29 to 1.71)	−0.63 (−1.86 to 0.6)
LABA/ICS vs LAMA	Moderate	−1.48 (-3.41 to 0.45)	−1.48 (-3.41 to 0.45)	−1.68 (−2.59 to −0.78)
LABA/ICS vs LABA	High	−1.00 (−2.61 to 0.61)	−1.00 (−2.61 to 0.61)	−0.67 (−1.88 to 0.54)
LAMA vs LABA	Moderate	1.84 (0.87 to 2.80)	1.84 (0.87 to 2.80)	1.01 (−0.2 to 2.22)
CFB in SGRQ at 6 months, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD (95% CI)**	**Pairwise, fixed-effect MD (95% CI)**	**NMA(fixed-effect/ fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ICS	Low	−0.99 (-4.12 to 2.14)	−0.99 (-4.12 to 2.14)	−0.22 (−1.28 to 0.82)
LABA/LAMA vs LAMA	Moderate	−1.20 (−1.83 to −0.57)	−1.20 (−1.83 to −0.57)	−1.18 (−1.8 to −0.56)

(*Continued*)

LABA/LAMA vs LABA	Moderate	−1.09 (−1.96 to −0.22)	−1.09 (−1.96 to −0.22)	−1.36 (−2.12 to −0.60)
LABA/ICS vs LAMA	NA	NA	NA	−0.96 (−1.98 to 0.09)
LABA/ICS vs LABA	Moderate	−1.18 (−1.97 to −0.40)	−1.18 (−1.97 to −0.40)	−1.14 (−1.90 to −0.37)
LAMA vs LABA	High	−0.25 (−1.09 to 0.58)	−0.23 (−0.99 to 0.54)	−0.18 (−0.91 to 0.55)
CFB in SGRQ at 12 months, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD (95% CI)**	**Pairwise, fixed-effect MD (95% CI)**	**NMA(fixed-effect/ fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ICS	NA	NA	NA	0.97 (0.48 to 2.42)
LABA/LAMA vs LAMA	Very low	−0.87 (−1.64 to −0.10)	−0.87 (−1.64 to −0.10)	−0.89 (−1.66 to −0.11)
LABA/LAMA vs LABA	High	−0.69 (−1.64 to 0.25)	−0.69 (−1.64 to 0.25)	−0.72 (−1.64 to 0.20)
LABA/ICS vs LAMA	NA	NA	NA	−1.85 (−3.28 to −0.43)
LABA/ICS vs LABA	Moderate	−1.70 (−2.82 to −0.58)	−1.70 (−2.82 to −0.58)	−1.69 (−2.81 to −0.57)
LAMA vs LABA	High	0.10 (−0.79 to 0.99)	0.10 (−0.79 to 0.99)	0.16 (−0.72 to 1.04)
TDI at 3 months, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD (95% CI)**	**Pairwise, fixed-effect MD (95% CI)**	**NMA(random-effects/ fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ICS	Low	0.40 (0.02 to 0.78)	0.36 (0.16 to 0.56)	0.35 (0.12 to 0.56)
LABA/LAMA vs LAMA	Moderate	0.48 (0.34 to 0.62)	0.48 (0.34 to 0.62)	0.54 (0.36 to 0.73)
LABA/LAMA vs LABA	Low	0.52 (0.31 to 0.74)	0.52 (0.31 to 0.74)	0.44 (0.20 to 0.67)
LABA/ICS vs LAMA	Very low	0.51 (−0.39 to 1.41)	0.51 (−0.39 to 1.41)	0.19 (−0.07 to 0.47)
LABA/ICS vs LABA	High	0.13 (−0.26 to 0.52)	0.09 (−0.20 to 0.37)	0.09 (−0.18 to 0.36)
LAMA vs LABA	Low	−0.18 (−0.63 to 0.27)	−0.06 (−0.26 to 0.14)	−0.10 (−0.36 to 0.14)

(*Continued*)

TDI at 6 months, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD (95% CI)**	**Pairwise, fixed-effect MD (95% CI)**	**NMA(fixed-effect/ fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ICS	High	0.13 (−0.24 to 0.51)	0.13 (−0.24 to 0.51)	0.15 (−0.10 to 0.40)
LABA/LAMA vs LAMA	Moderate	0.32 (0.17 to 0.46)	0.32 (0.17 to 0.46)	0.33 (0.18 to 0.47)
LABA/LAMA vs LABA	Moderate	0.40 (0.23 to 0.57)	0.40 (0.23 to 0.57)	0.37 (0.21 to 0.52)
LABA/ICS vs LAMA	NA	NA	NA	0.18 (−0.09 to 0.45)
LABA/ICS vs LABA	High	0.21 (−0.09 to 0.50)	0.21 (−0.09 to 0.50)	0.22 (−0.02 to 0.46)
LAMA vs LABA	Low	0.00 (−0.17 to 0.18)	0.00 (−0.17 to 0.18)	0.04 (−0.12 to 0.21)
TDI at 12 months, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD (95% CI)**	**Pairwise, fixed-effect MD (95% CI)**	**NMA(fixed-effect/ fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ICS	NA	NA	NA	NA
LABA/LAMA vs LAMA	Moderate	0.22 (0.11 to 0.34)	0.22 (0.11 to 0.34)	0.20 (0.09 to 0.32)
LABA/LAMA vs LABA	Very low	0.42 (0.06 to 0.77)	0.30 (0.17 to 0.42)	0.30 (0.17 to 0.42)
LABA/ICS vs LAMA	NA	NA	NA	NA
LABA/ICS vs LABA	NA	NA	NA	NA
LAMA vs LABA	High	0.15 (−0.11 to 0.40)	0.06 (−0.05 to 0.18)	0.09 (−0.02 to 0.21)
CFB in FEV1 at 3 months, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD (95% CI)**	**Pairwise, fixed-effect MD (95% CI)**	**NMA random-effects/ fixed-class) MD (95% CrI)**
LABA/LAMA vs LABA/ICS	Low	0.08 (0.03 to 0.12)	0.03 (0.02 to 0.04)	0.05 (0.03 to 0.07)
LABA/LAMA vs LAMA	Low	0.07 (0.06 to 0.09)	0.07 (0.06 to 0.08)	0.08 (0.06 to 0.09)
LABA/LAMA vs LABA	Very low	0.07 (0.03 to 0.12)	0.04 (0.03 to 0.05)	0.09 (0.07 to 0.11)
LABA/ICS vs LAMA	Low	0.02 (−0.02 to 0.06)	0.06 (0.05 to 0.07)	0.02 (0 to 0.04)
LABA/ICS vs LABA	Moderate	0.05 (0.04 to 0.06)	0.05 (0.04 to 0.06)	0.03 (0.01 to 0.05)

(*Continued*)

LAMA vs LABA	Low	−0.00 (−0.02 to 0.02)	−0.00 (−0.01 to 0.00)	0.01 (−0.01 to 0.03)
CFB in FEV1 at 6 months, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD (95% CI)**	**Pairwise, fixed-effect MD (95% CI)**	**NMA(random-effects/ fixed-class) MD[a] (95% CrI)**
LABA/LAMA vs LABA/ ICS	High	0.10 (0.05 to 0.15)	0.10 (0.05 to 0.15)	0.05 (0.03 to 0.08)
LABA/LAMA vs LAMA	Low	0.06 (0.05 to 0.07)	0.06 (0.05 to 0.07)	0.06 (0.05 to 0.08)
LABA/LAMA vs LABA	Moderate	0.07 (0.06 to 0.08)	0.07 (0.06 to 0.08)	0.08 (0.06 to 0.09)
LABA/ICS vs LAMA	High	−0.00 (−0.06 to 0.06)	−0.00 (−0.06 to 0.06)	0.01 (−0.02; 0.04)
LABA/ICS vs LABA	Moderate	0.04 (0.01 to 0.07)	0.04 (0.01 to 0.07)	0.02 (−0.01 to 0.05)
LAMA vs LABA	Very low	0.02 (0.00 to 0.03)	0.02 (0.01 to 0.03)	0.01 (0.00 to 0.03)
CFB in FEV1 at 12 months, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects MD (95% CI)**	**Pairwise, fixed-effect MD (95% CI)**	**NMA(fixed-effect/ random-class) MD (95% CrI)**
LABA/LAMA vs LABA/ ICS	NA	NA	NA	NA
LABA/LAMA vs LAMA	Very low	0.06 (0.04 to 0.08)	0.05 (0.04 to 0.06)	0.06 (−0.01 to 0.12)
LABA/LAMA vs LABA	Very low	0.07 (0.06 to 0.09)	0.07 (0.06 to 0.08)	0.08 (0.02 to 0.14)
LABA/ICS vs LAMA	NA	NA	NA	NA
LABA/ICS vs LABA	NA	NA	NA	NA
LAMA vs LABA	Very low	0.02 (0.01 to 0.03)	0.02 (0.01 to 0.03)	0.02 (0.00 to 0.06)
Mortality, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMAm (fixed-effect/ fixed-class) OR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	1.06 (0.35 to 3.23)	1.13 (0.42 to 3.04)	1.25 (0.79 to 2.00)
LABA/LAMA vs LAMA	Moderate	0.98 (0.66 to 1.43)	0.96 (0.67 to 1.39)	0.91 (0.63 to 1.32)
LABA/LAMA vs LABA	Moderate	1.19 (0.68 to 2.09)	1.15 (0.68 to 1.95)	1.16 (0.75 to 1.81)
LABA/ICS vs LAMA	Moderate	0.48 (0.06 to 3.82)	0.43 (0.06 to 2.96)	0.73 (0.45 to 1.16)

(*Continued*)

LABA/ICS vs LABA	Moderate	0.93 (0.76 to 1.15)	0.93 (0.76 to 1.15)	0.93 (0.76 to 1.14)
LAMA vs LABA	Moderate	1.30 (0.75 to 2.25)	1.23 (0.74 to 2.07)	1.28 (0.83 to 1.98)
Total SAEs, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(fixed-effect/ fixed-class) OR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	0.88 (0.64 to 1.22)	0.88 (0.67 to 1.16)	0.91 (0.78 to 1.05)
LABA/LAMA vs LAMA	High	1.03 (0.91 to 1.16)	1.03 (0.92 to 1.15)	1.03 (0.93 to 1.15)
LABA/LAMA vs LABA	High	1.06 (0.91 to 1.22)	1.06 (0.91 to 1.22)	1.02 (0.91 to 1.15)
LABA/ICS vs LAMA	Moderate	0.93 (0.49 to 1.77)	0.93 (0.49 to 1.76)	1.14 (0.98 to 1.32)
LABA/ICS vs LABA	Low	1.17 (0.92 to 1.47)	1.13 (1.00 to 1.28)	1.13 (1.01 to 1.27)
LAMA vs LABA	High	1.01 (0.88 to 1.15)	1.01 (0.88 to 1.15)	0.99 (0.88 to 1.11)
COPD SAEs, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(fixed-effect/ fixed-class) OR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Low	0.80 (0.39 to 1.64)	0.81 (0.50 to 1.31)	0.96 (0.75 to 1.22)
LABA/LAMA vs LAMA	High	0.96 (0.79 to 1.17)	0.96 (0.79 to 1.17)	0.99 (0.82 to 1.19)
LABA/LAMA vs LABA	Moderate	1.08 (0.83 to 1.40)	1.09 (0.84 to 1.41)	0.92 (0.75 to 1.13)
LABA/ICS vs LAMA	Moderate	1.02 (0.21 to 4.99)	1.00 (0.22 to 4.41)	1.04 (0.81 to 1.32)
LABA/ICS vs LABA	High	0.95 (0.83 to 1.04)	0.95 (0.80 to 1.12)	0.96 (0.82 to 1.13)
LAMA vs LABA	Low	0.91(0.65 to 1.27)	0.96 (0.77 to 1.21)	0.93 (0.76 to 1.14)
Cardiac SAEs, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(fixed-effect/ fixed-class) OR[a] (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	0.90 (0.43 to 1.89)	0.91 (0.45 to 1.83)	1.28 (0.91 to1.81)
LABA/LAMA vs LAMA	Moderate	1.09 (0.82 to 1.45)	1.08 (0.82 to 1.42)	1.05 (0.80 to 1.36)
LABA/LAMA vs LABA	Moderate	1.19 (0.69 to 2.07)	1.28 (0.88 to 1.88)	1.24 (0.92 to1.68)

(*Continued*)

LABA/ICS vs LAMA	Moderate	0.16 (0.02 to 1.34)	0.14 (0.02 to 1.13)	0.82 (0.58 to 1.15)
LABA/ICS vs LABA	High	0.97 (0.78 to 1.21)	0.98 (0.79 to 1.21)	0.97 (0.79 to 1.19)
LAMA vs LABA	Moderate	1.16 (0.83 to 1.61)	1.19 (0.86 to 1.65)	1.19 (0.89 to 1.59)
Dropouts due to AEs, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(fixed-effect/ fixed-class) OR (95% CrI)**
LABA/LAMA vs LABA/ ICS	Low	0.90 (0.68 to 1.19)	0.91 (0.69 to 1.19)	0.99 (0.83 to 1.18)
LABA/LAMA vs LAMA	Low	1.12 (0.96 to 1.31)	1.13 (0.97 to 1.31)	1.09 (0.95 to 1.26)
LABA/LAMA vs LABA	Very low	0.94 (0.68 to 1.29)	0.93 (0.76 to 1.14)	0.91 (0.78 to 1.06)
LABA/ICS vs LAMA	Low	0.78 (0.35 to 1.71)	0.80 (0.44 to 1.47)	1.11 (0.92 to 1.33)
LABA/ICS vs LABA	Moderate	0.90 (0.77 to 1.06)	0.90 (0.77 to 1.06)	0.92 (0.80 to 1.06)
LAMA vs LABA	Moderate	0.90 (0.73 to 1.10)	0.89 (0.75 to 1.05)	0.84 (0.72 to 0.97)
Pneumonia, low-risk	**Certainty of evidence in the pairwise MA**	**Pairwise, random-effects OR (95% CI)**	**Pairwise, fixed-effect OR (95% CI)**	**NMA(random-effectsIP/fixed-class) OR[a] (95% CrI)**
LABA/LAMA vs LABA/ ICS	Moderate	0.43 (0.19 to 0.97)	0.42 (0.19 to 0.92)	0.61 (0.34 to 1.01)
LABA/LAMA vs LAMA	Moderate	1.23 (0.84 to 1.81)	1.26 (0.88 to 1.79)	1.23 (0.82 to 1.84)
LABA/LAMA vs LABA	Moderate	1.54 (0.95 to 2.49)	1.60 (1.01 to 2.53)	1.18 (0.75 to 1.81)
LABA/ICS vs LAMA	Low	5.82 (0.70 to 48.80)	5.90 (0.71 to 49.14)	2.02 (1.16 to 3.72)
LABA/ICS vs LABA	High	1.64 (1.25 to 2.14)	1.64 (1.26 to 2.14)	1.93 (1.29 to 3.22)
LAMA vs LABA	Moderate	1.01 (0.61 to 1.69)	1.02 (0.64 to 1.61)	0.96 (0.62 to 1.49)

[a]Potential inconsistency in the date. Results should be interpreted with caution
AE: adverse event; **CFB:** change from baseline; **HR:** hazard ratio; **FEV1:** forced expiratory volume in one second;**ICS:** inhaled corticosteroid; **LABA:** long-acting beta2-agonist; **LAMA:** long-acting muscarinic antagonist; **MA:** meta-analysis; **MD:** mean difference; **NA:** not applicable; **NMA:** network meta-analysis; **OR:** odds ratio; **SAE:** serious adverse event; **SGRQ:** St George's Respiratory Questionnaire; **TDI:** Transition Dyspnoea Index

CONTRIBUTIONS OF AUTHORS

Yuji Oba extracted data, assessed studies for methodological quality, constructed figures and tables for pairwise meta-analyses and otherwise constructed the review. Sofia Dias and Edna Keeney conducted the network meta-analyses, constructed figures, and drafted the network meta-analysis results. All authors contributed to the writing of the review and approved the final version of the document.

DECLARATIONS OF INTEREST

Yuji Oba: none known

Edna Keeney: none known

Namratta Ghatehorde: none known

Sofia Dias: Pfizer Portugal, Novartis and Boehringer Ingelheim have paid fees to the University of Bristol for seminars. Sofia Dias is a co-applicant on a grant by which Pfizer is partially sponsoring a researcher (not herself).

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes for the review.

1. We included free combinations of long-acting β-agonist/long-acting muscarinic antagonist (LABA/LAMA) and LABA/inhaled corticosteroid (ICS).

2. We added intraclass/group comparisons (e.g. LAMA versus LAMA, LABA versus LABA) in the NMAs.

3. We added network meta-analyses (NMAs) for individual treatment effects for all outcomes.

4. We used a newly developed, shared parameter model for exacerbation outcomes.

5. We used odds ratios for dichotomous outcomes in the NMAs instead of hazard ratios after reviewing time-to-event data in the existing clinical studies.

6. We used a binominal likelihood with a logit instead of cloglog link for dichotomous outcomes in the NMAs.

7. We cautioned readers instead of grading a level of evidence or restricting the analysis to a subset of studies in the NMAs when we suspected an imbalance in effect modifiers between clinical studies.

8. We chose the simplest model for the NMAs when the difference in deviance information criterion (DIC) was less than 3 points between models rather than choosing a model based on heterogeneity in the pairwise comparison.

9. We did not perform a meta-regression analysis to explore potential sources of heterogeneity due to complexity of the data and models.

10. We included primary outcomes and pneumonia only in the 'Summary of findings' tables rather than all outcomes as planned.